Synthesis S. G. Pharande Review

Synthesis of Lactams via Isocyanide-Based Multicomponent Reactions

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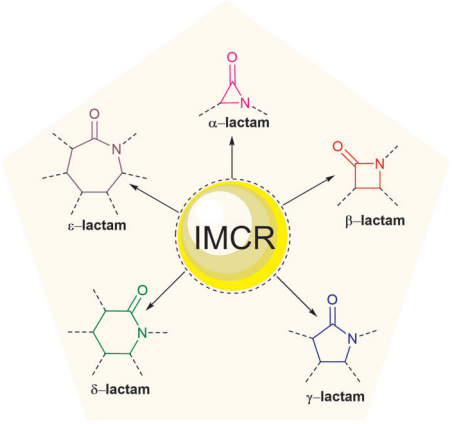
This review is dedicated to Albert Einstein



Received: 16.05.2020
Accepted after revision: 22.08.2020
Published online: 07.10.2020
DOI: 10.1055/s-0040-1706297; Art ID: ss-2020-z0268-r

Abstract Lactams are very important heterocycles as a result of their presence in a wide range of bioactive molecules, natural products and drugs, and also due their utility as versatile synthetic intermediates. Due to these reasons, numerous efforts have focused on the development of effective and efficient methods for their synthesis. Compared to conventional two-component reactions, multicomponent reactions (MCRs), particularly isocyanide-based MCRs, are widely used for the synthesis of a range of small heterocycles including lactam analogues. Despite their numerous applications in almost every field of chemistry, as yet there is no dedicated review on isocyanide-based multicomponent reactions (IMCRs) concerning the synthesis of lactams. Therefore, this review presents strategies towards the synthesis of α-, β-, γ-, δ- and ε-lactams using IMCRs or IMCRs/post-transformation reactions reported in the literature between 2000 and 2020.

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Key words lactam synthesis, isocyanides, isocyanide-based multicomponent reactions, post-transformations, cyclic amides

1 Introduction

Since the discovery of the penicillin antibiotics **1** (Figure 1) by Alexander Fleming,[1] β-lactams and their analogues have become very important in numerous areas of medicinal chemistry and drug discovery. Lactams are cyclic amides that are generally categorized based on their ring size. The three-, four-, five, six- and seven-membered rings are named α-lactam **2** (also known as 2-aziridinones), β-lactam **3** (2-azetidinones), γ-lactam **4** (2-pyrrolidinones), δ-lactam **6** (2-piperidinones) and ε-lactam **7** (2-azepanones or caprolactam), respectively (Figure 1).

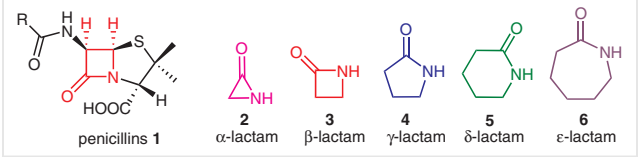

Figure 1 General structure of penicillin **1** and ring variants of lactam heterocycles **2–6**

Lactams are recognized as a privileged class of heterocycles, and apart from their antibiotic properties,[2] this core is present in many bioactive molecules. Many lactam-containing compounds possess useful biological activity, specifically with three- to seven-membered-ring lactams representing some of the most important. Examples of such activity are β-lactamase inhibition, cholesterol absorption inhibition,[3a] antimicrobial,[3b–d] antifungal,[4] antimalarial,[5] anti-HIV,[6] anticancer,[7] anti-inflammatory,[8] antidepressant,[9] antiviral,[10] DPP-4 inhibition[11] and anticonvulsant.[12] Additionally, lactams are very important structural motifs present in several natural products such as the penicillins **1** (Figure 1), nocardicin A (**7**), monobactam (**8**), tabtoxin (**9**), pseurotin A (**10**), dysidin (**11**), sintokamides A–E (**12**), malingamide A (**13**), strychnine (**14**), adalinine (**15**), corydaidine (**16**), caprolactin A (**17**), isobenganamide E (**18**) and bengamide K (**19**) (Figure 2).[13]

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β-Lactams constitute a major class of antibiotics and contribute to more than 50% of the global antibiotics market. However, due to increasing antibacterial resistance toward β-lactam antibiotics,[14] the scientific community has been forced to move its focus from four-membered lactam rings to other larger-ring lactam analogues. In this context, in 1986, two independent research groups reported for the first time the synthesis of γ-lactam-based antibiotics.[15] Unfortunately, none of them showed prominent biological activity as antibacterials or as β-lactamase inhibitors. However, these results encouraged many academics and industrial researchers to plan synthetic routes to develop new bioactive compounds containing larger ring-sized analogues of β-lactam. As a result, numerous synthetic methodologies have been described for the synthesis of β-lactams and their analogues.

Of the various approaches towards lactams, the isocyanide-based multicomponent reaction (IMCR) is one of the most diverse, versatile, and widely used methods.[16] The first IMCR was described by Passerini in 1921 involving a three-component reaction between carboxylic acids, oxo compounds, and isocyanides to afford α-acyloxy carboxamides in one-step.[17] This reaction was further expanded by Ugi et al. in 1959 as a four-component variant by using amines as the fourth component to give a diamide product.[18] Shortly after, the same group reported the first synthesis of a β-lactam using their reaction methodology.[19] IMCRs, especially Ugi-four component (Ugi-4CR) and Ugi-three component reactions (Ugi-3CR), are perfectly suited for the synthesis of lactam-like small molecules since they allow the construction of complex products using small and simple building blocks in a single operation, or may lead to a product containing multifunctional groups which can be

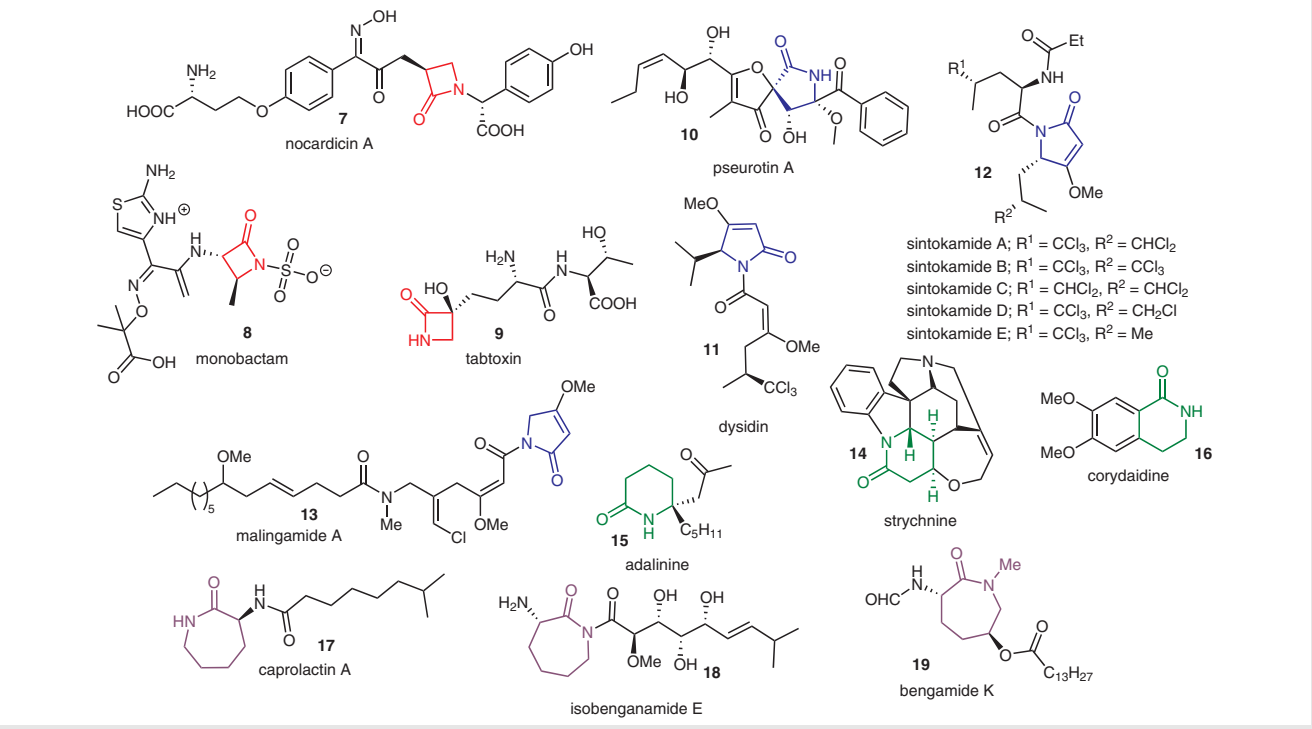
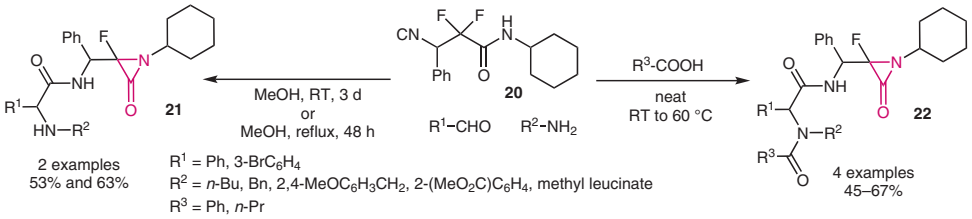


Figure 2 Natural products containing a lactam core

Biographical Sketch

Shrikant G. Pharande was born in Maharashtra, India in 1987. He obtained his B.Sc. and M.Sc. degrees (Tuljaram Chaturchand College, Baramati) in chemistry from Pune University. Later, he worked as a research assistant at the National Chemical Laboratory, Pune with Dr. Hanumant Borate and Dr. Vandana Pore for two years. In 2014, he started his doctoral studies under the supervision of Professor Dr. Rocio Gámez-Montaño at the University of Guanajuato, Guanajuato, Mexico and received his Ph.D. degree in 2018.



Scheme 1 Synthesis of monofluorinated α-lactams **21** and **22**

used as a substrate for another complexity-generating reaction.[20] Also, during the Ugi reaction an intramolecular Mumm rearrangement occurs resulting in the facile formation of small cyclic products via ring closure.

In the last two decades, several articles discussing the formation of a variety of lactams via IMCRs have been published, thus illustrating their importance in various fields of interest, particularly in medicinal chemistry. However, there is no single dedicated review that describes the synthesis of α-, β-, γ-, δ- and ε-lactams using IMCRs. Thus, the present review specifically focuses on the synthesis of the abovementioned five classes of lactams containing only a single amide bond via IMCR or IMCR/post-transformation strategies, and excludes synthetic methods towards the synthesis of lactams possessing bis-amide bonds such as diketopiperazines. This review covers the major contributions from the literature between 2000 and 2020, with minor exceptions, and describes only three to seven-membered ring-sized lactams.

2 Developments in Lactam Synthesis

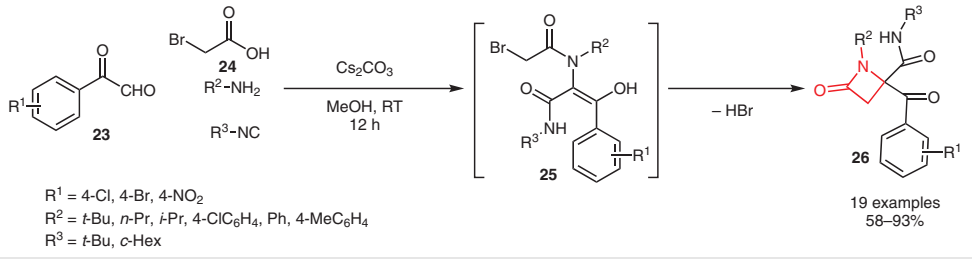
2.1 α-Lactams

An α-lactam is a highly strained three-membered heterocycle which can undergo ring-opening in the presence of any nucleophile. For these reasons, their facile and efficient synthesis has been a challenge for many organic chemists. Traditionally α-lactams are prepared by cyclization of α-haloamides mediated by a strong base,[21] however, unwanted side reactions resulting from the use of a strong base are always a concern. In this context, Qian and co-workers reported[22] the base-free synthesis of monofluorinated α-lactams **21** and **22** via a one-pot IMCR followed by an intramolecular cyclization strategy (Scheme 1). A small series of α-lactam products **22** was prepared in moderate to good yields of 45–67% via the Ugi-4CR between *gem*-difluoromethylene isocyanide **20** with aldehydes, amines, and acids followed by dehydrofluorination under solvent-free heating conditions. On the other hand, α-lactam **21** was synthesized via an Ugi-3CR/intramolecular cyclization in MeOH at room temperature or under reflux conditions.

2.2 β-Lactams

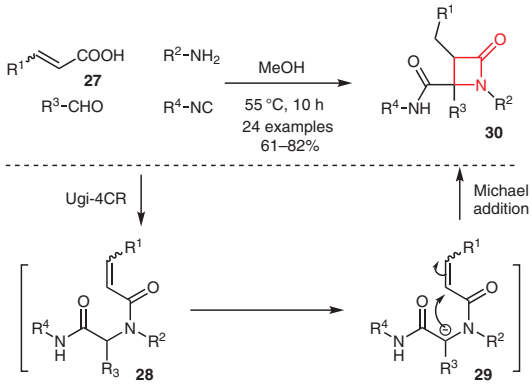
Ding and co-workers[23] developed an efficient route for the synthesis of β-lactams **26** in moderate to excellent yields via a one-pot Ugi-4CR/S_N cyclization strategy (Scheme 2). The authors reacted substituted phenyl glyoxal **23** and α-bromocarboxylic acid (**24**) with various amines and isocyanides to give Ugi intermediate **25** along with β-lactam **26** in low yield. The intramolecular substitution happened with the release of HBr and resulted in a drop of pH from 7 to 4. Thus, the authors used Cs_2CO_3 as a base to neutralize the reaction solution (pH 6) and to trigger the substitution reaction to give the final products **26** in higher yields.

Lu and co-workers[24] reacted maleic or fumaric acid **27** with aldehydes, isocyanides, and amines to give β-lactams **30** via a one-pot Ugi-4CR/intramolecular Michael addition in methanol at 55 °C (Scheme 3). According to DFT calculations, this reaction prefers a Michael addition path by generating anion **29** from Ugi adduct **28** instead of an aza-Michael route.[25] Furthermore, based on theoretical calculations, the authors noted that the diastereoselectivity was



Scheme 2 Ugi-4CR/S_N cyclization to obtain β-lactams **26**

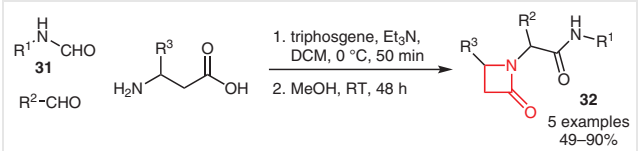
controlled by the Michael addition step. The advantage of this methodology is its robustness for synthesizing medicinally important β-lactams in one pot under mild conditions.



R^1 = CO_2Me, CO_2Et
R^2 = 4-MeC_6H_4, 4-ClC_6H_4, *n*-Pr, 4-$O_2NC_6H_4$
R^3 = 2-Py, 2-thiazole, 2-imidazole, 5-(3-phenylisoxazole), C=OPh, CO_2Et
R^4 = *t*-Bu, *c*-Hex, Bn, *n*-Bu

Scheme 3 Synthesis of β-lactams **30**

Five examples concerning the synthesis of β-lactams **32** from bifunctional β-amino acids via an isocyanide-less IMCR method have been described (Scheme 4).[26] The authors synthesized diverse formamides **31** by using a modified Leuckart–Wallach procedure, which were further converted in situ into isocyanides and reacted in the same pot with the respective aldehyde and β-amino acid via an Ugi-3CR to afford β-lactams **32** in moderate to excellent yields (49–90%). This new method resulted in higher yields of the desired products in shorter reaction times compared to the traditional method.

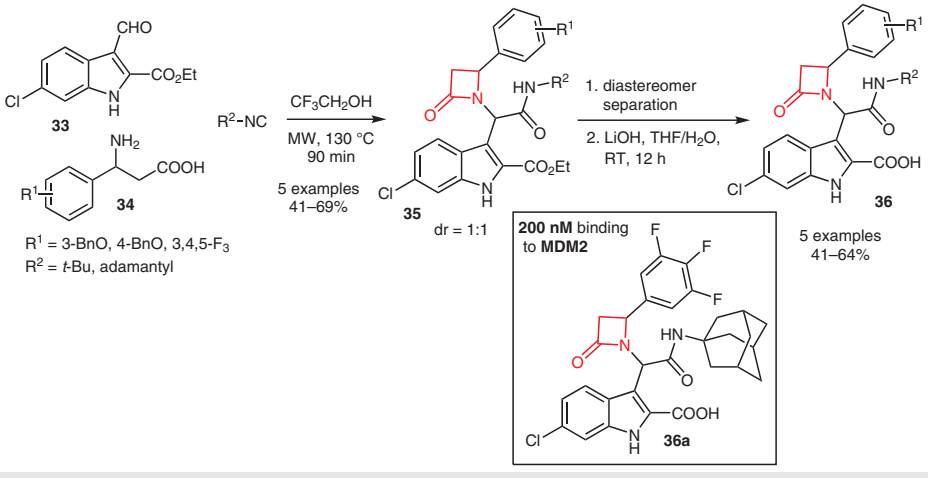


R^1 = *c*-Hex, 4-$MeC_6H_4CH_2$, 4-$F_3COC_6H_4CH_2$, 4-$NCC_6H_4CH_2$, -$(CH_2)_5CO_2Me$
R^2 = 4-BrC_6H_4, 3-BrC_6H_4, 4-NCC_6H_4, 4-*i*-PrC_6H_4, 2,5-$(MeO)_2C_6H_3$
R^3 = H, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 4 Synthesis of β-lactams via an isocyanide-less IMCR

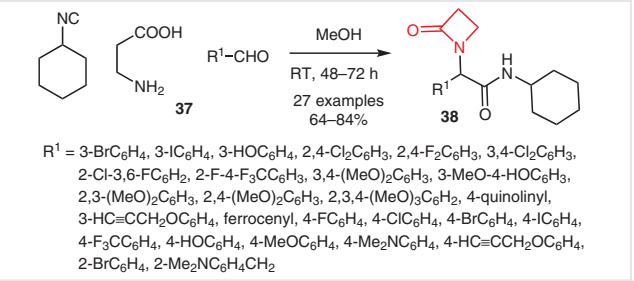
AnchorQuery, a build on scaffold-hopping technique,[27] is a pharmacophore-based virtual screening platform which allows the rapid and efficient screening of chemical libraries.[28] With the help of AnchorQuery, the research group of Dömling reported[29] the synthesis of β-lactams **36** in moderate to good yields via a two-step microwave-assisted Ugi-3CR followed by diastereomeric separation and hydrolysis (Scheme 5). The multicomponent reaction between aldehyde **33**, substituted amino acid **34**, and an isocyanide at 130 °C under microwave irradiation resulted in the formation of β-lactam Ugi adduct **35** in a 1:1 diastereomeric ratio, which upon diastereomeric separation followed by ester hydrolysis using LiOH gave lactam **36**. All the synthesized β-lactams were examined for their MDM2 receptor binding affinities using computational modeling methods. Among them, compound **36a** was found to be the more potent with a 200 nM binding affinity to the MDM2 receptor.

The group of Blackie has employed an Ugi-3CR to synthesize β-lactams **38** in good to excellent yields (64–84%) by using β-alanine (**37**), cyclohexyl isocyanide and a variety of aromatic aldehydes in MeOH at room temperature.[30] All the Ugi products are racemic mixtures and were screened in an *in vitro* assay against the chloroquine-sensitive D10 strain of *Plasmodium falciparum*. All the tested compounds showed low to moderate antimalarial activity (Scheme 6).



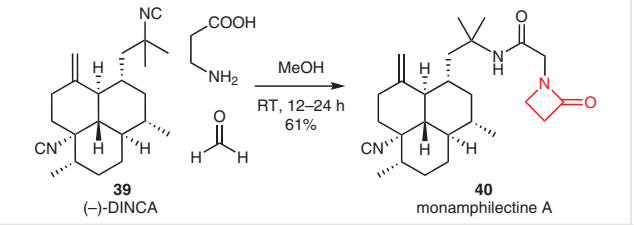
R^1 = 3-BnO, 4-BnO, 3,4,5-F_3
R^2 = *t*-Bu, adamantyl

Scheme 5 Synthesis of β-lactams **36**



Scheme 6 Synthesis of β-lactams **38** via an Ugi-3CR using β-alanine (**37**)

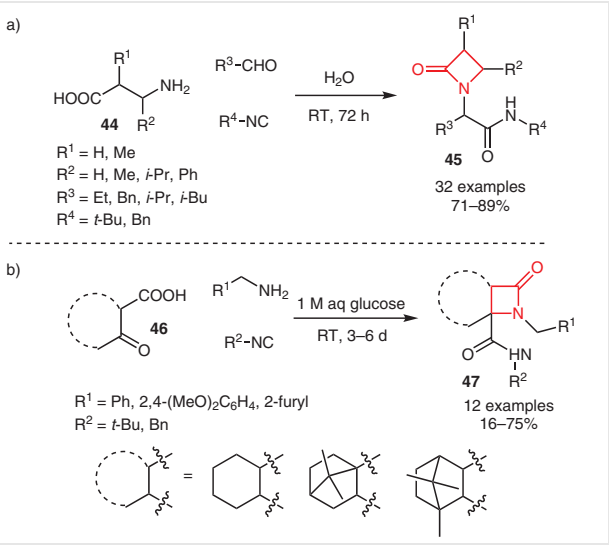
Rodríguez and Avilés discovered that the extracts of some marine sponges from Mona Island (Puerto Rico) exhibited antiplasmodial and antimycobacterial activity.[31] Large-scale organic extraction of 200 g of the dried sponge *Svenzea flava* using a 1:1 mixture of $CHCl_3$–MeOH resulted in the isolation of 3 mg of the diterpenoid β-lactam alkaloid monamphilectine A (**40**), along with 528 mg of the sesquiterpene isocyanide (–)-DINCA (**39**).[32] To confirm the relative and absolute configuration, and to investigate its bioactivity, a semisynthesis of monamphilectine A (**40**) was successfully performed in 61% yield via an Ugi-3CR of β-alanine, formaldehyde and isocyanide **39** in MeOH (Scheme 7).[31] Both, monamphilectine A (**40**) and (–)-DINCA showed dual *in vitro* activity against the chloroquine-resistant W2 strain of *P. falciparum* (IC_{50}: 0.60 μM and 0.04 μM) and *M. tuberculosis* H37Rv (MIC values: 15.3 μg/mL and 3.2 μg/mL), respectively.



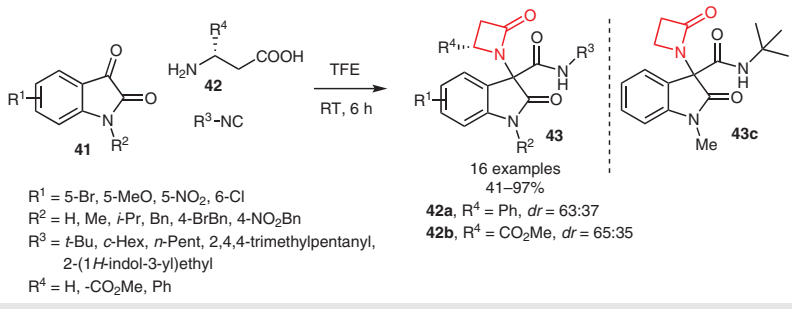
Scheme 7 Semisynthesis of the diterpenoid β-lactam alkaloid **40** via an Ugi-3CR

Silvani and co-workers[33] developed a strategy for the synthesis of β-lactam-core-linked oxindoles **43** via an Ugi-3CR using isatins **41**, isocyanides, and β-amino acids **42** in a one-pot manner (Scheme 8). When chiral β-amino acids **42a** and **42b** were used, enantiomerically pure β-lactam diastereoisomers **43a** (dr = 63:37) and **43b** (dr = 65:35) were obtained as the products, the relative stereochemistries of which were determined by X-ray analysis. Further, all the synthesized products were screened for antibacterial activity, however, only compound **43c** showed weak activity.

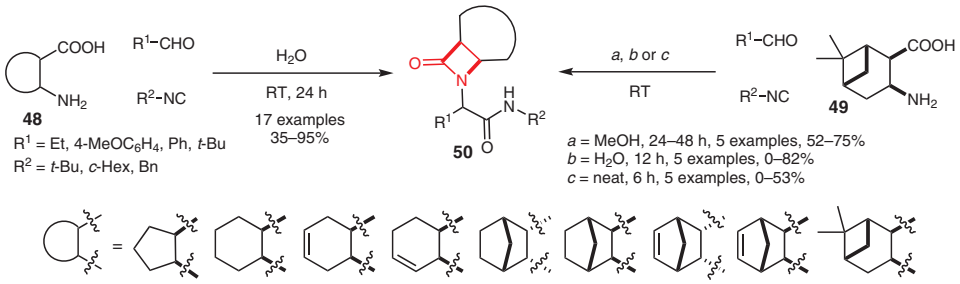
The Ugi reaction can be carried out efficiently under aqueous conditions to give products in high yields.[34] Pirrung and Sarma[35] developed an Ugi-3CR using either substituted or unsubstituted β-amino acids **44** and a variety of aldehydes and isocyanides to give β-lactams **45** in good to excellent yields (71–89%) using water as a green solvent (Scheme 9, a). All the products were isolated by extraction with high HPLC purity (70–99%). The same research group disclosed Ugi-3CR methodology to synthesize a series of acyclic and fused cyclic β-lactams **47** using β-keto acids **46** in 1 M aqueous glucose solution as a non-ionic solvent (Scheme 9, b).[36] It was noted that due to the additional ring



Scheme 9 Synthesis of β-lactams via Ugi-3CRs in (a) water, and (b) 1 M aqueous glucose solution as a non-ionic solvent



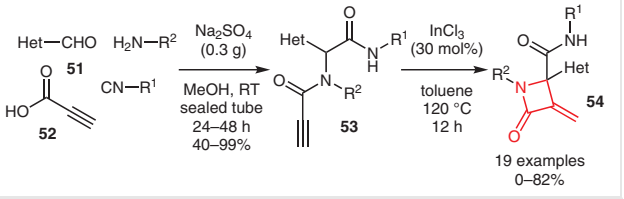
Scheme 8 Synthesis of β-lactam-containing 3,3-disubstituted oxindoles **43** via an Ugi-3CR



Scheme 10 Synthesis of bi- and tricyclic β-lactams **50** via an Ugi-3CR

strain generated by four-membered lactams in the case of cyclic β-keto acids, lower yields were obtained with prolonged reaction times (6 days) compared to the acyclic β-keto acids (3 days).

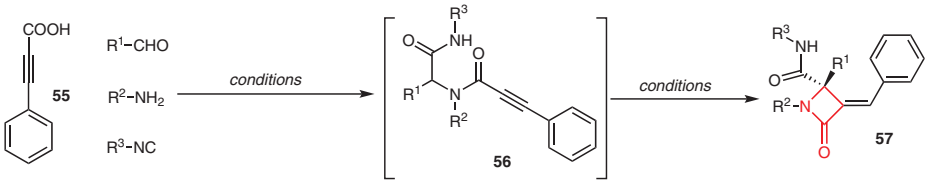
In the same vein, a water-mediated synthetic route for the synthesis of bi- and tricyclic β-lactams **50** was developed by Fülöp and co-workers[37] using racemic cyclic β-amino acids **48** with aldehydes and isocyanides via an Ugi-3CR (Scheme 10). The use of water as a solvent was found to be advantageous over organic solvents as all the products were isolated in high yields by either filtration or extraction.[38] The concentration of water in the reaction played an important role in the formation of the product. Additionally, the same research group developed an Ugi-3CR methodology to synthesize enantiopure tricyclic β-lactams using (1*R*,2*R*,3*S*,4*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid (**49**).[39] A comparative study of the effect of the reaction medium on the yields and time of the reaction was performed. A similar set of reactions was carried out in MeOH, in water and under neat conditions. The reactions in water were found to be more efficient and more rapid than in MeOH or under neat conditions.



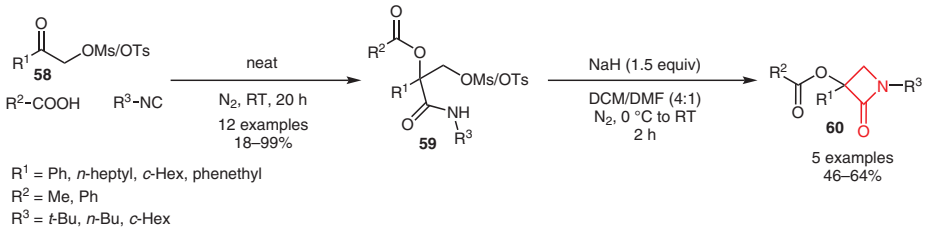
Scheme 11 Synthesis of heterocycle-linked α-methylene β-lactams **54** via Ugi-4CR/intramolecular addition reactions

α-Methylene β-lactam represents one type of important building block with numerous applications in the synthesis of medicinally active molecules and natural products.[40] Van der Eycken and co-workers have reported the synthesis of heterocycle-linked α-methylene β-lactams **54** in yields of up to 82% by employing Ugi adducts **53** containing substituted terminal alkynes in In(III)-catalyzed intramolecular addition reactions (Scheme 11).[41] The adducts **53** were obtained by reacting heterocyclic aldehydes **51**, acid **52**, isocyanides, and amines via an Ugi-4CR in a sealed tube.

Balalaie and co-workers demonstrated an efficient route for the synthesis of β-lactams **57** in good to excellent yields (63–95%) via a one-pot Ugi-4CR/base-mediated cyclization reaction (Scheme 12).[42] A variety of aromatic and heteroaromatic aldehydes worked well in the reaction and gave excellent yields of the final products **57**. Further, X-ray crystallographic data confirmed the *E*-configuration of the double bond. In 2018, Srivastava and co-workers[43] synthesized a similar series of β-lactams **57** by using an identical one-pot Ugi-4CR/intramolecular cyclization methodology starting from phenylpropiolic acid (**55**), aldehydes, isocyanides and amines to obtain Ugi adducts **56**. This was followed by treatment with sodium hydride to facilitate the intramolecular cyclization resulting in the formation of β-lactams **57** (Scheme 12). These authors screened all their synthesized



Scheme 12 Synthesis of β-lactams **57** via Ugi-4CR/cyclization reactions

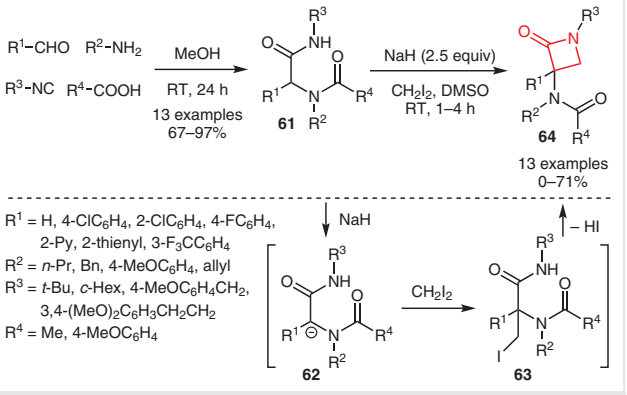


Scheme 13 Synthesis of β-lactams **60**

β-lactams against the histamine-3 receptor (H3R), however, none of them were found to be active.

α-Substituted sulfonyloxy ketones **58** are efficient substrates for the synthesis of β-lactams **60** via a two-step Passerini-3CR followed by base-mediated cyclization (Scheme 13).[44] The solvent-free reactions of compounds **58** with isocyanides and acids under a nitrogen atmosphere resulted in the formation of Passerini adducts **59** in quantitative yields. The adducts **59** were readily converted into β-lactams **60** via intramolecular cyclization in the presence of NaH (1.5 equiv). It was claimed that the sulfonyl ketone **58** underwent the Passerini condensation more rapidly than the parent aryl or aliphatic ketone.

In 2017, El Kaïm and co-workers[45] disclosed a novel two-step method towards the synthesis of β-lactams **64** via an Ugi-4CR followed by base-mediated [3+1] cyclization of amide dianions using diiodomethane (Scheme 14). The authors reacted aldehydes, amines, isocyanides, and acids under conventional Ugi-4CR conditions to afford Ugi adducts **61** in up to quantitative yields, which under strongly basic



Scheme 14 Synthesis of β-lactams **64**

conditions in the presence of diiodomethane were converted into β-lactams **64** at room temperature. The optimization studies revealed that 2.5 equivalents of NaH in DMSO were sufficient for the reaction between adduct **61** and CH_2I_2 to give the expected cyclized product **64**. It was suggested, by DFT calculations, that anion **62** first reacts with CH_2I_2 to give iodomethyl Ugi intermediate **63**, which then undergoes an intramolecular cyclization to yield product **64**.

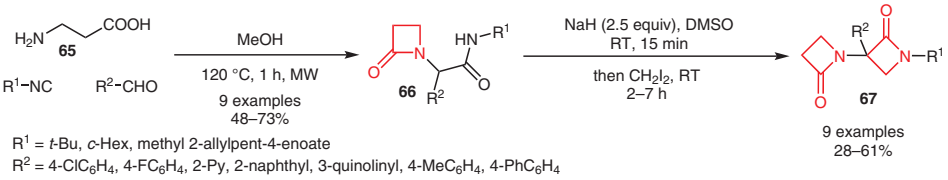
Later, in 2019, El Kaïm[46] reported the two-step synthesis of bis β-lactams **67** in poor to good yields (28–61%) via an Ugi-3CR followed by a base-mediated diiodomethane cyclocondensation reaction at room temperature (Scheme 15). The amino acid **65** on reaction with an isocyanide and an aldehyde at 120 °C under microwave irradiation was readily converted into β-lactam **66**. Next, NaH–CH_2I_2-based cyclocondensation afforded bis β-lactam **67**. Also, it was demonstrated that two consecutive β-lactam formations could be achieved under one-pot conditions with comparable yields. All the synthesized bis β-lactams were screened for antibacterial activity against *Escherichia coli* MC4100, *Staphylococcus aureus* subsp. *aureus* ATCC6538 and *Micrococcus luteus* ATCC9341 strains, however, none of them were found to be active.

2.3 γ-Lactams

Due to the availability of a large number of IMCR-based reports for the synthesis of γ-lactams, this section has been further subdivided into sections for a more detailed insight.

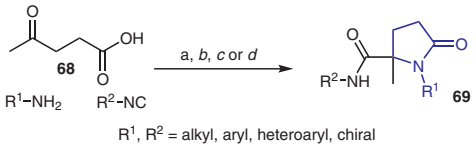
2.3.1 General γ-Lactams

In 2004, Tye and Whittaker[47] reported a rapid and efficient synthesis of γ-lactams **69** in poor to excellent yields



Scheme 15 Synthesis of bis β-lactams **67**

(17–90%) via Ugi-3CRs of levulinic acid (**68**), amines, and isocyanides under MW heating conditions (Scheme 16, conditions *a*). The authors used a design of experiments (DoE) approach for rapid reaction optimization. It was claimed that this methodology enabled the synthesis of γ-lactams in just 30 minutes compared to the traditional process,[48] which required 48 hours. In the same vein, Mironov and co-workers[49] published a method to synthesize similar γ-lactams **69** using water and surfactant solutions as solvents (Scheme 16, conditions *b*). Mironov reported that even less soluble substrates reacted readily and gave the final γ-lactam products in good yields. In a parallel investigation, the rapid synthesis of γ-lactams **69** was reported by Deprez and co-workers[50] by employing acid **68** with a variety of isocyanides and amines under solvent-free microwave conditions (Scheme 16, conditions *c*). Quantitative yields (15 examples, 83–96%) were obtained in the majority of cases in just 3 minutes of reaction time. It was claimed that improved yields of cyclized products were obtained under MW heating compared to conventional methods. Similarly, in 2004, Krelaus and Westermann[51] synthesized γ-lactams **69** in poor to excellent yields via Ugi-3CRs using bifunctional acid **68** and isocyanides along with chiral and achiral amines (Scheme 16, conditions *d*).

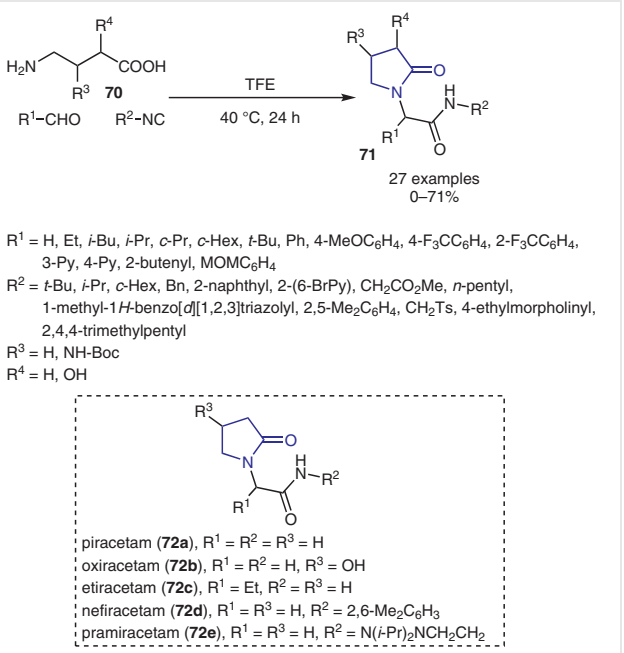


conditions: *a:* MeOH, MW, 100 °C, 30 min, 8 examples (17–90%) *Tye and Whittaker*
b: H_2O, RT, 16–45 h, 5 examples (65–89%) *Mironov et al.*
c: neat, MW, 100 °C, 3 min, 15 examples (83–96%) *Deprez et al.*
d: MeOH, RT, 48 h, 10 examples (7–93%) *Krelaus and Westermann*

Scheme 16 Syntheses of γ-lactams **69**

γ-Lactams **72a–e** (Scheme 17), popularly known as racetams, are a large class of drugs used in the treatment of epilepsy, dementia, depression, anxiety, and hypoxia.[52] Thus, inspired by the medicinal importance of these small molecules and by the lack of simple and versatile methods towards their synthesis, the research group of Orru[53] published a mild and efficient method for the synthesis of γ-lactams **71** by employing amino acids **70**, aldehydes, and isocyanides in an Ugi-3CR in TFE at 40 °C (Scheme 17). The authors prepared 27 examples of γ-lactams **71** by utilizing this methodology, including the successful syntheses of piracetam (**72a**) (58%), etiracetam (**72c**) (53%), nefiracetam (**72d**) (39%) and pramiracetam (**72e**) (quantitative yield).

Cotinine (**73**), a predominant metabolite of nicotine (**74**), is an important γ-lactam with a wide range of pharmacological properties.[54] Inspired by its diverse medicinal properties, in 2015, Vazquez and co-workers[55] developed a two-step Ugi-4CR/post-condensation strategy for the synthesis of highly substituted cotinine and iso-cotinine ana-

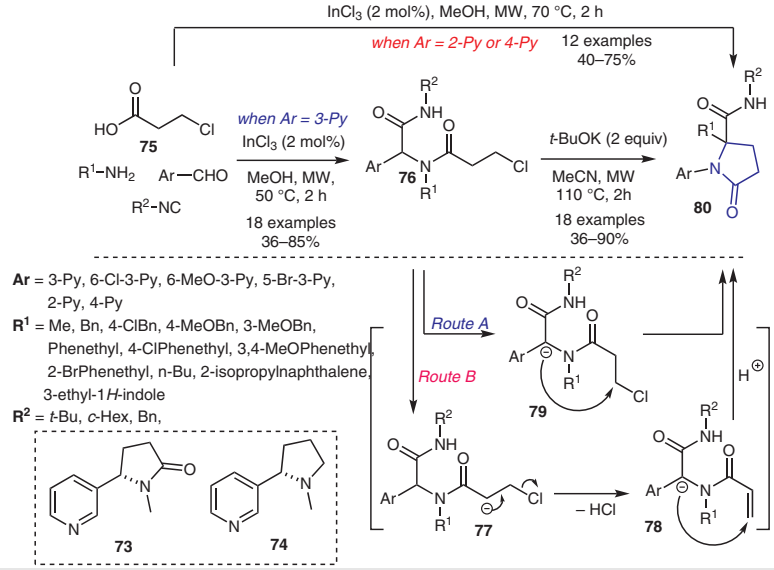


Scheme 17 Synthesis of γ-lactams **71** and **72a,c–e**

logues **80** (Scheme 18). First, an $InCl_3$-catalyzed multicomponent reaction was performed between 3-chloropropionic acid (**75**), 3-pyridine aldehyde, amines, and isocyanides to afford Ugi adducts **76**, which subsequently gave γ-lactams **80** in moderate to excellent yields via *t*-BuOK-mediated cyclization under MW heating conditions. However, when pyridine-2(4)-carboxaldehydes were used, lactams **80** were obtained directly without the use of a base at a slightly elevated temperature. It was claimed that the slightly basic nature of the reaction medium due to the presence of a primary amine and a pyridine moiety facilitates anion generation by abstracting a highly acidic peptidyl proton adjacent to the 2- or 4-pyridinecarboxaldehyde, followed by intramolecular cyclization to give the final products in one step. The mechanism proposed by the authors suggests that the intramolecular cyclization might proceed via two routes (Scheme 18).[55] Either a base-mediated S_N2 process via intermediate **79** to give the cyclized product (route A), or in situ formation of Michael acceptor **78** from intermediate **77** followed by nucleophilic addition to generate the cyclic product **80** (route B). However, according to Baldwin's rules, the 5-*endo*-*trig* cyclization of intermediate **78** is disfavored and thus the reaction is less likely to follow route B.

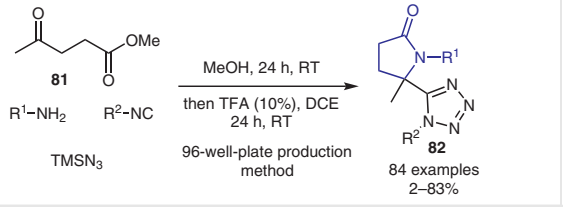
In a parallel investigation, the synthesis of indole-linked γ-lactams **80** [where Ar = 2-(1*H*-indole)] via a two-step Ugi-4CR followed by a K_2CO_3-mediated S_N2 cyclization in DMF at 100 °C was reported by Shiri and co-workers.[56]

In 2012, Hulme and co-workers[57] developed a one-pot, two-step methodology for the synthesis of 1,5-disubstituted-tetrazole-linked γ-lactams **82** by reacting keto-ester



Scheme 18 Synthesis of highly substituted γ-lactams **80**

methyl levulinate **81** with isocyanides, $TMSN_3$ and a wide range of primary amines via an Ugi-4CR to afford Ugi adducts, which were subsequently cyclized under acidic conditions to give the final cyclized products **82** in poor to excellent yields (Scheme 19). A large library of γ-lactam products **82** was prepared by using a 96-well plate production method.



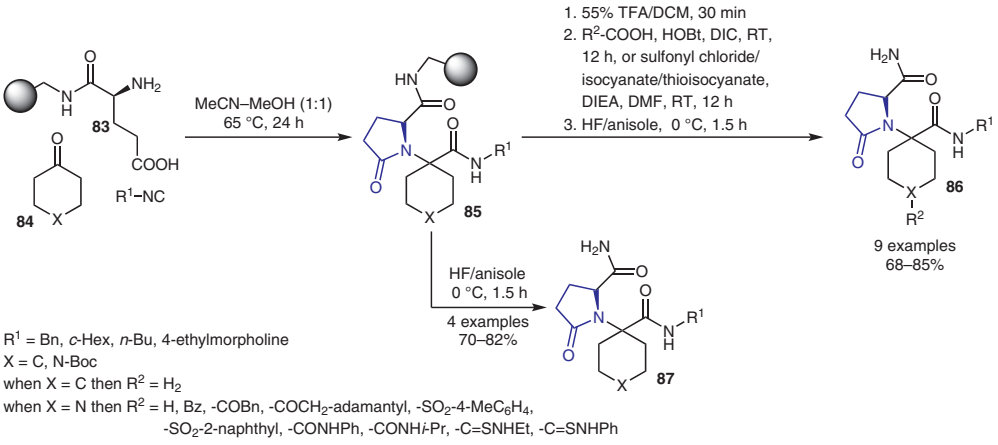
Scheme 19 Synthesis of 1,5-disubstituted-tetrazole-linked γ-lactams **82**

Solid-phase organic synthesis is a powerful synthetic tool that is used widely in the synthesis of complex bioactive molecules.[58] In 2010, Liu and Nefzi[59] reported the synthesis of enantiopure N-substituted γ-lactams **86** via solid-phase synthesis (Scheme 20). Bifunctional polymer-supported glutamic acid **83** was reacted with cyclohexanone or Boc-piperidone **84** and an isocyanide via an Ugi-3CR under heating conditions to generate resin-supported Ugi adducts **85**, which upon cleavage of the solid support gave enantiopure γ-lactams **87** in excellent yields. Further, in order to increase the complexity and diversity, the authors synthesized N-substituted γ-lactam analogues **86**. First, deprotection of Ugi adducts **85** was carried out followed by amidation using various carboxylic acids, sulfonyl chlorides, isocyanates, or thioisocyanates. Finally, cleavage of the resin gave γ-lactams **86** in excellent yields.

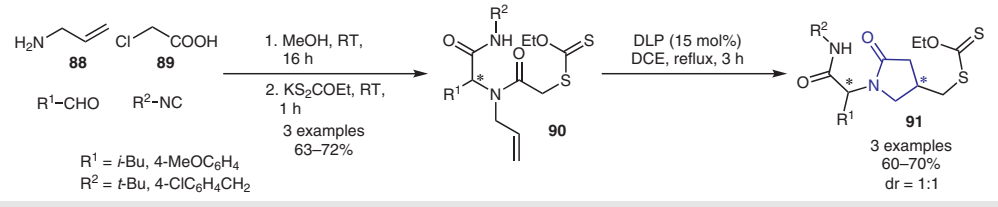
El Kaïm and co-workers[60] have developed a two-step process for the synthesis of γ-lactams **91** using an Ugi-4CR followed by a radical cyclization (Scheme 21). In this transformation, initially allylamine (**88**), chloroacetic acid (**89**), aldehydes, and isocyanides were reacted together to form an Ugi adduct. This was followed by the addition of KS_2COEt resulting in the generation of Ugi-xanthate adducts **90** in good yields after 1 hour at room temperature. Adducts **90** were readily converted into the expected γ-lactam products **91** as 1:1 mixtures of separable diastereoisomers via 5-*exo*-*trig* cyclization by heating under radical cyclization conditions in the presence of 15 mol% of dilauroyl peroxide (DLP) as a radical initiator.

Later, in 2010, El Kaïm and colleagues extended the scope of the above-mentioned reaction by using propargyl amine (**92**), instead of allylamine (**88**), and stoichiometric amounts of DLP to obtain β-methylene γ-lactams **94** from adducts **93** under slightly modified Ugi-4CR/reductive radical cyclization conditions (Scheme 22).[61]

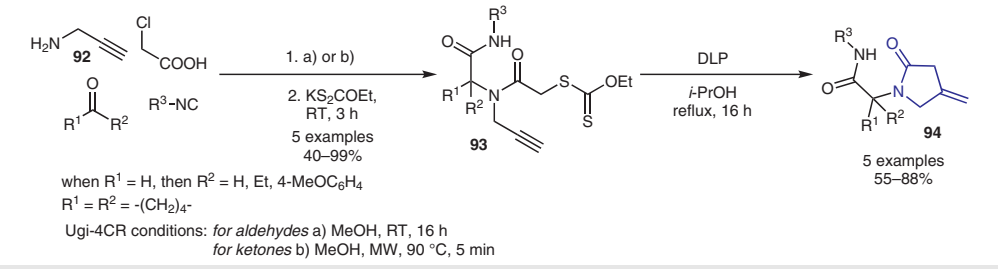
A two-step synthesis of enamide γ-lactams **97** via an Ugi-4CR followed by a base-mediated propargylation reaction has also been reported (Scheme 23).[62] First, Ugi adducts **95** were prepared in good to excellent yields (67–95%) via Ugi-4CRs of aldehydes, amines, isocyanides, and carboxylic acids. Next, the adducts **95** underwent alkylation mediated by NaH (2.5 equiv) with propargyl bromide (**96**) in the presence of TBAF followed by formation of enamide γ-lactams **97** through cyclization of an amide with an alkyne. It was noted that TBAF played an important role as an additive



Scheme 20 Synthesis of enantiopure γ-lactams **87** and N-substituted γ-lactams **86** via solid-phase synthesis



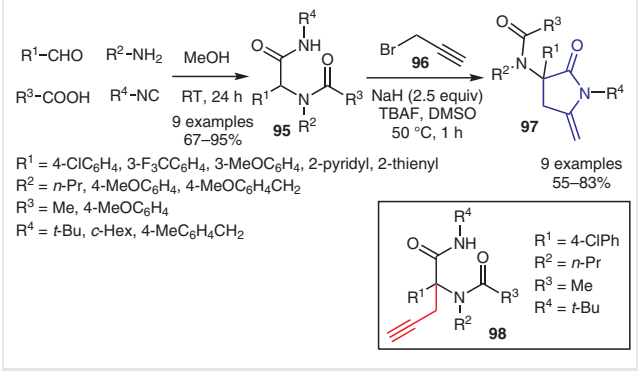
Scheme 21 Synthesis of γ-lactams **91** using an Ugi-4CR followed by radical cyclization



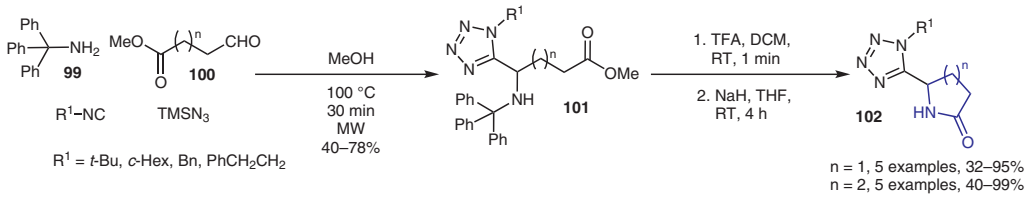
Scheme 22 Synthesis of β-methylene γ-lactams **94**

in the formation of cyclic products **97** and lower equivalents of NaH (1 equiv) resulted in the formation of alkylated product **98** (51%) along with the recovery of unreacted Ugi adduct **95** (32%).

Dömling and co-workers[63] developed a fast and efficient methodology for the synthesis of 1,5-disubstituted tetrazolo γ- and δ-lactams **102** in moderate to excellent yields via Ugi–azide reactions followed by a deprotection and cyclization strategy (Scheme 24). Adduct **101** was readily prepared by treatment of trityl amine (**99**) with aliphatic aldehyde **100**, an isocyanide and $TMSN_3$ at 100 °C under MW irradiation. The adduct **101** was further converted into lactam **102** by trityl group deprotection followed by base-mediated cyclization. It was noted that due to the steric hindrance generated by the trityl moiety, the Ugi reactions only proceed-



Scheme 23 Synthesis of enamide γ-lactams **97**

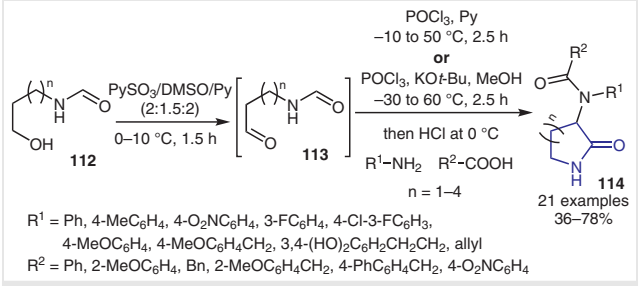


Scheme 24 Synthesis of unsubstituted tetrazolo γ- and δ-lactams **102** via Ugi–azide reactions

ed under MW heating and only aliphatic aldehydes were well tolerated. Additionally, protein data bank analysis of these γ- and δ-lactams revealed the presence of strong tridirectional H-bond donor–acceptor interactions with the amino acids of the binding sites.

Recently, Polindara-García and co-workers developed[64] an efficient microwave-assisted two-step method for the synthesis of highly substituted γ-lactams **107** via an Ugi-4CR followed by a radical cyclization–oxyamination process promoted by ammonium persulfate and TEMPO (**106**) (Scheme 25). First, the Ugi-4CR was performed utilizing acid **103**, aldehyde **104**, an amine, and an isocyanide in the presence of $InCl_3$ (2 mol%) in a MW at 70 °C to afford 1,3-dicarbonyl Ugi adducts **105** in excellent yields. Next, as a result of thermal homolytic cleavage an anion radical species **108** was generated from $(NH_4)S_2O_8$, which upon single-electron transfer (SET) with Ugi adduct **105** gave radical **110** and ammonium hydrogen sulfate (**109**). Subsequently, radical **110** was readily converted into cyclized radical **111** via intramolecular 5-*exo*-*trig* cyclization onto the alkene. Finally, radical–radical coupling between **111** and TEMPO (**106**) resulted in the formation of the final γ-lactam **107**. All the isolated products were obtained in moderate to poor (82:18 to 49:51) diastereomeric ratios.

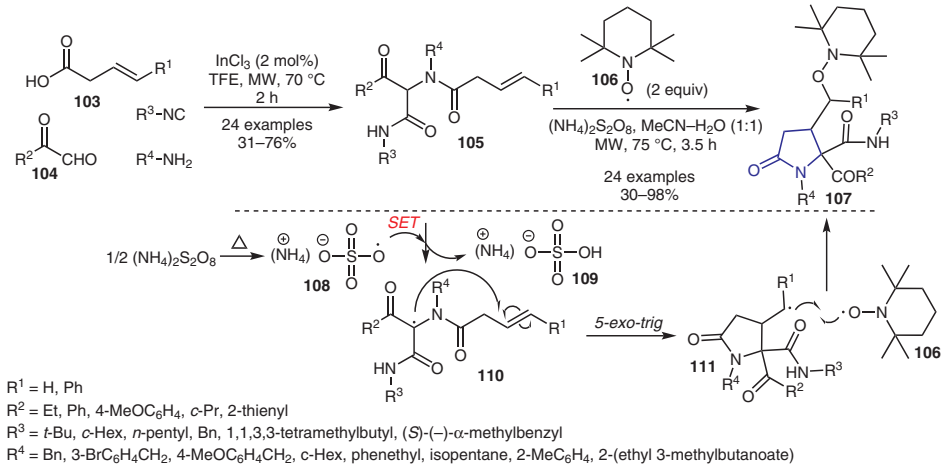
In 2012, Khan and Saxena[65] published the synthesis of a series of lactams **114** in moderate to excellent yields via a one-pot Parikh–Doering oxidation/dehydration/Ugi cyclization (Scheme 26). The reaction employed *N*-formylated aminols **112**, which underwent oxidation to yield intermediates **113**. Dehydration followed by condensation with an amine and an acid through an Ugi-3CR resulted in the formation of cyclized lactams **114**. The authors reported 21 examples using this strategy, including the syntheses of five- to eight-membered lactams.



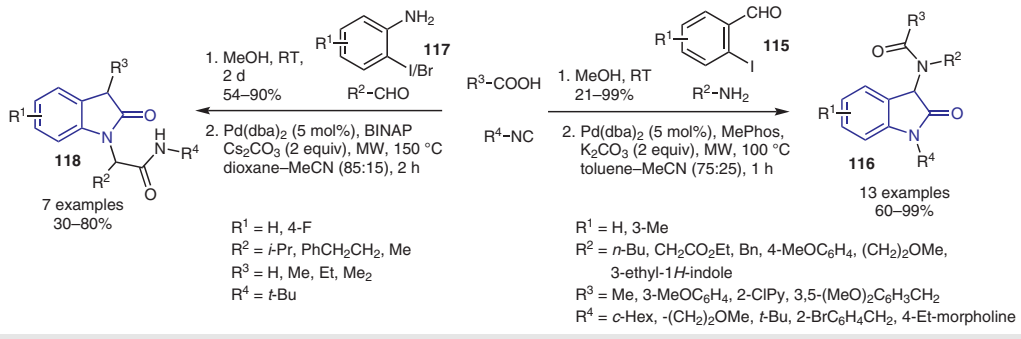
Scheme 26 Synthesis of a series of lactams **114**

2.3.2 Benzo-Fused γ-Lactams

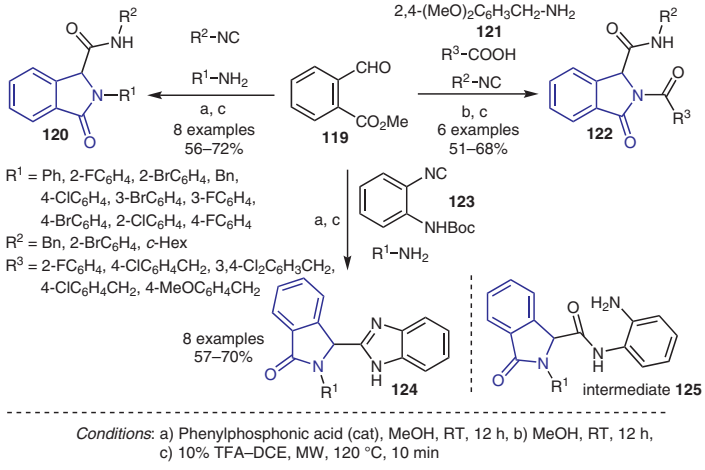
In 2006, Zhu and co-workers[66] reported the synthesis of benzo-fused γ-lactams **116** via a two-step process involving an Ugi-4CR followed by a palladium-catalyzed intramolecular Buchwald–Hartwig reaction (Scheme 27). Initially the functionalized *ortho*-substituted iodobenzaldehydes **115** were reacted with amines, carboxylic acids, and isocya-



Scheme 25 Synthesis of highly substituted γ-lactams **107**



Scheme 27 Synthesis of benzo fused γ-lactams **116** and **118** via Ugi-4CR/palladium-catalyzed intramolecular Buchwald–Hartwig reactions

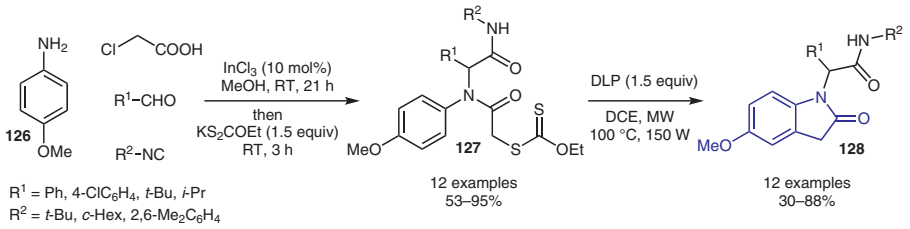


Scheme 28 Synthesis of benzo-fused γ-lactam analogues **120**, **122**, and **124**

nides in MeOH at room temperature to give Ugi products in 21–99% yield. These Ugi adducts were subsequently treated in the presence of $Pd(dba)_2$ as the catalyst and MePhos as the ligand at 100 °C under microwave heating conditions to obtain the final cyclized products **116** in high yields. It was noted that microwave heating not only accelerated the reaction rate but also improved the efficiency of the intramolecular Buchwald–Hartwig coupling reaction. The advantage of this method is that a variety of functional groups such as esters, amines, and ethers, and heterocycles such as pyridine and indole were well tolerated. Additionally, in 2009, Zhu and colleagues[67] reported Ugi-4CRs followed by Pd-catalyzed intramolecular α-CH arylation of amides to give benzo-fused γ-lactams **118** in moderate to excellent yields, which are structural analogues of γ-lactams **116**. The authors treated *ortho*-halo-substituted anilines **117** with an aldehyde, a carboxylic acid, and an isocyanide to form Ugi adducts, which then underwent intramolecular cyclization using BINAP as the ligand under otherwise previously reported identical conditions to yield the final products **118** (Scheme 27).

Methyl 2-formylbenzoate (**119**) is an important bifunctional starting material. Chen and co-workers[68] reported the synthesis of three types of benzo-fused γ-lactam analogues, **120**, **122**, and **124**, by using common aldehyde **119** in an Ugi-MCR followed by intramolecular amidation (Scheme 28). Initially the Ugi-3CR between aldehyde **119**, an isocyanide, and an amine was carried out in the presence of catalytic phenylphosphonic acid to afford Ugi adducts, which then underwent intramolecular cyclization under acidic conditions at 120 °C in a MW to generate benzo-fused γ-lactams **120**. The synthesis of **122** was achieved by performing an Ugi-4CR utilizing amine **121** followed by cyclization via removal of the 2,4-dimethoxybenzyl group under microwave irradiation and acidic conditions. Similarly, benzimidazole-linked benzo-fused γ-lactam **124** analogues were prepared via Ugi-3CRs using Boc-protected isocyanide **123** to yield intermediate **125** via the Ugi product and Boc deprotection followed by amidation under acidic conditions. It is important to note that all the analogues were prepared in one-pot processes.

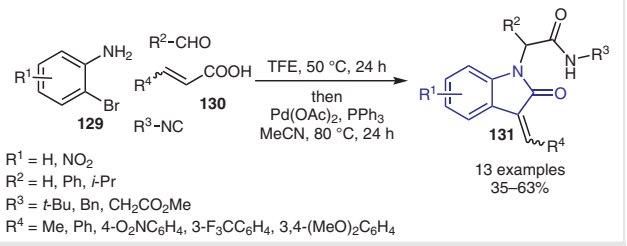
Dithiocarbonates or xanthates are widely used in organic synthesis due to their unique ability to store reactive radicals in a dormant form.[69a] In 2014, Gámez-Montaño's re-



Scheme 29 Synthesis of benzo-fused γ-lactams **128** via free-radical cyclization

search group[69b] employed *p*-anisidine (**126**), chloroacetic acid, aldehydes and isocyanides followed by potassium ethyl xanthogenate (KS_2COEt) to prepare xanthates **127** via a one-pot $InCl_3$-catalyzed Ugi-4CR followed by an S_N2 process. The xanthates then undergo free-radical cyclization to afford the final benzo-fused γ-lactams **128** by using dilauroyl peroxide (DLP) as a free-radical initiator and oxidant. DFT-based calculations were performed to support the kinetics and thermodynamics of the xanthate-mediated free-radical cyclization (Scheme 29).

In 2006, highly substituted benzo-fused γ-lactams **131** were synthesized in moderate to good yields via a one-pot Ugi-4CR/Heck reaction (Scheme 30).[70] The 2-bromoanilines **129** underwent an Ugi-4CR with aldehydes, isocyanides, and a variety of acrylic acids **130** to give the corresponding Ugi adducts. Heating these adducts in the presence of $Pd(OAc)_2$ (3 mol%) and PPh_3 (6 mol%) afforded benzo-fused γ-lactams **131** as isomeric mixtures through an intramolecular Heck cyclization.

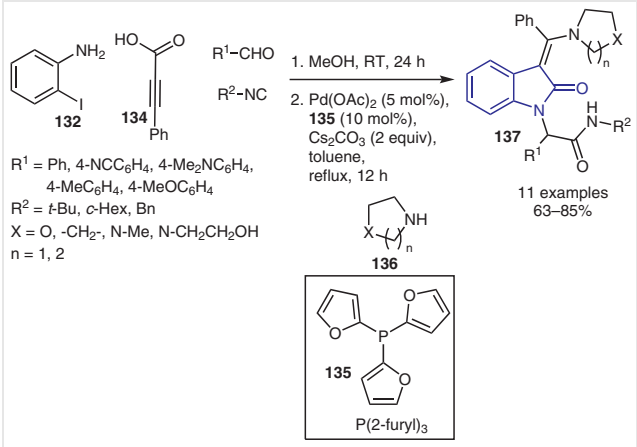


Scheme 30 Synthesis of highly substituted benzo-fused γ-lactams **131**

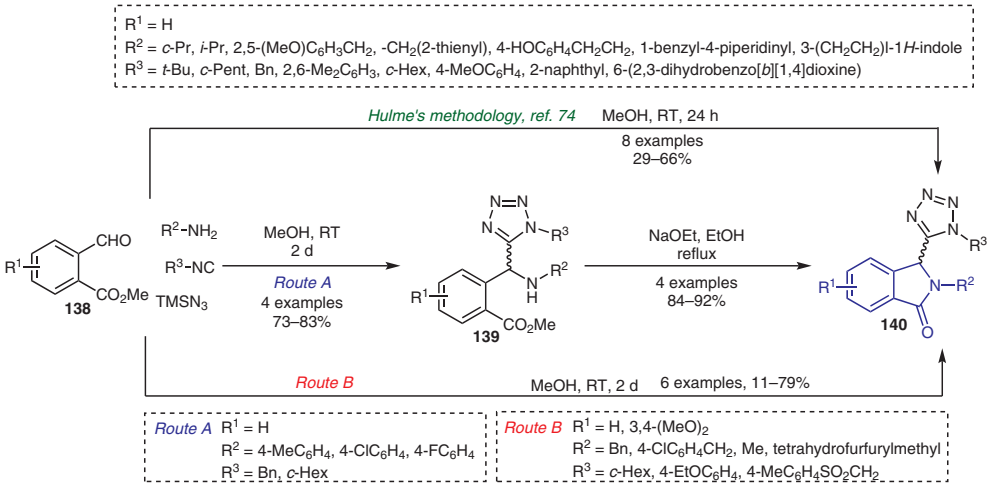
In 2011, Balalaie and co-workers[71] described an efficient palladium-catalyzed Ugi-carbopalladative cyclization–Buchwald methodology for the synthesis of benzo-fused γ-lactams **137** (Scheme 31). Treatment of 2-iodoaniline (**132**) with phenylpropiolic acid (**134**), aldehydes and isocyanides gave Ugi adducts through an Ugi-4CR. The formed Ugi adducts then underwent a domino carbopalladative cyclization–Buchwald reaction initiated by the addition of cyclic secondary amines **136** in the presence of $Pd(OAc)_2$ as the catalyst and tri(2-furyl)phosphine (**135**) as the ligand in toluene under reflux conditions to afford benzo-fused γ-lactams **137** in excellent yields (63–85%). It was noted that all the products formed with *Z*-configuration of the double bond, as confirmed by NMR studies.

The tetrazole moiety is found in various bioactive and pharmaceutically important molecules.[72] In 2008, Marcaccini et al.[73] reported the synthesis of 1,5-disubstituted-tetrazole-linked benzo-fused γ-lactams **140** via an Ugi-4CR followed by cyclization (Scheme 32). It was claimed that the reaction can proceed via two routes based on the nature of the amine source used. When anilines were used as the amine source, the reaction follows route A, where initially the Ugi adducts **139** (73–83%) were formed, and subsequent base-mediated cyclization resulted in the formation of benzo-fused γ-lactams **140** in excellent yields. On the other hand, when alkyl and benzylic amines were used, the reaction proceeded through route B to give directly the final cyclized products **140** without any base in a one-pot manner. Later, in 2013, Hulme's research group[74] reported the synthesis of similar benzo-fused γ-lactam analogues **140** in moderate to good yields under the conventional Ugi–azide reaction conditions at room temperature (Scheme 32). Also, these authors synthesized an additional 96 analogues using a 24-well plate method, however, in the majority of cases, poor yields were obtained.

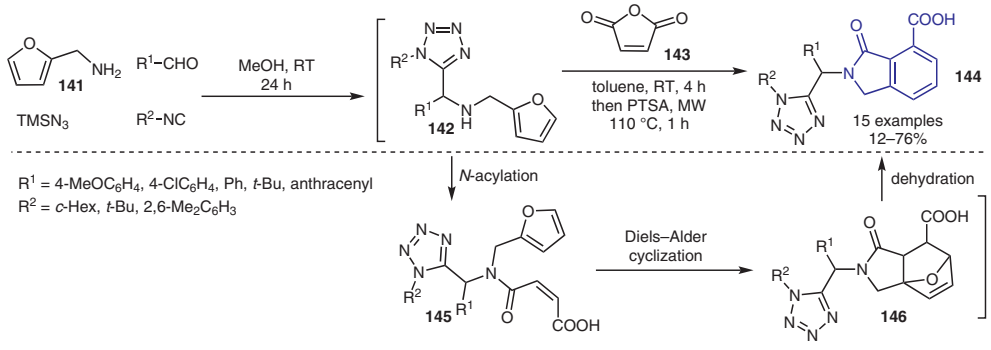
In 2006, Gámez-Montaño and co-workers[75] reported the synthesis of 1,5-disubstituted-tetrazole-linked benzo-fused γ-lactams **144** in 12–76% yields under mild conditions via a one-pot Ugi-azide/(*N*-acylation/*exo*-Diels–Alder)/aromatization–dehydration strategy (Scheme 33). The Ugi-tetrazole adducts **142** were synthesized by reacting furan-2-ylmethanamine (**141**), aldehydes, isocyanides, and



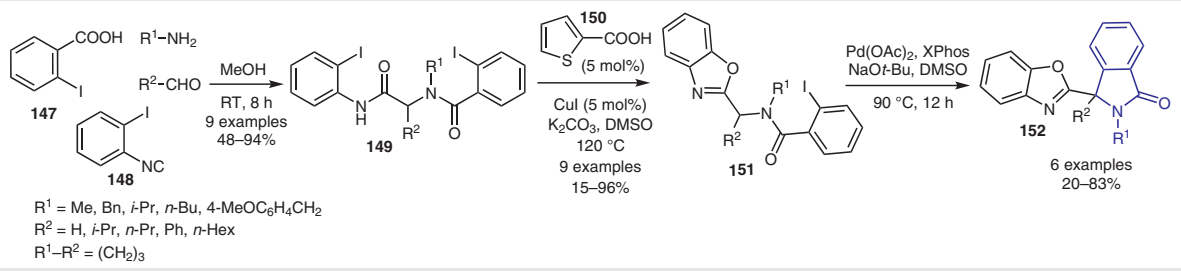
Scheme 31 Synthesis of benzo-fused γ-lactams **137**



Scheme 32 Synthesis of 1,5-disubstituted-tetrazole-linked benzo-fused γ-lactams **140**



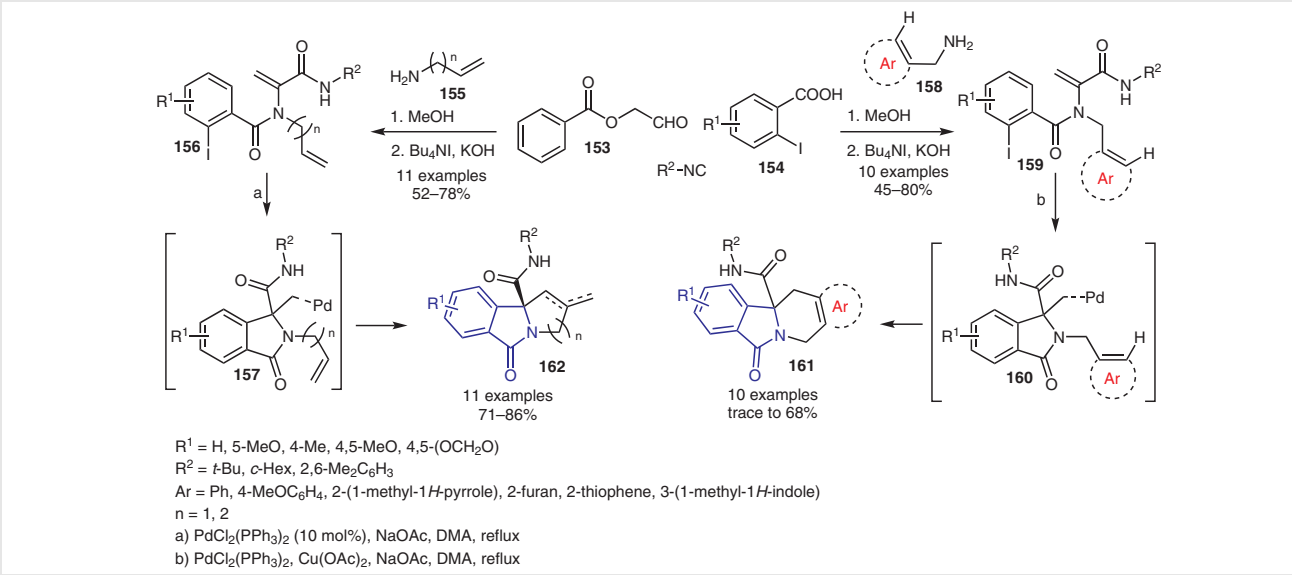
Scheme 33 Synthesis of 1,5-disubstituted-tetrazole-linked benzo-fused γ-lactams **144**



Scheme 34 Synthesis of benzoxazole-linked benzo-fused γ-lactams **152**

$TMSN_3$ in MeOH, which on reaction with maleic anhydride (**143**) in toluene underwent *N*-acylation to give intermediates **145**. The acid intermediates **145** were readily converted into cycloadducts **146** via an intramolecular Diels–Alder reaction. For the formation of the final aromatized products **144**, PTSA (3 equiv) was used under MW heating conditions in dry toluene. The sequential mechanism proposed by the authors was supported by DFT calculations.

Zhu and co-workers,[76] in 2008, reported the synthesis of benzoxazole-linked benzo-fused γ-lactams **152** via a three-step Ugi-4CR followed by regiospecific sequential intramolecular Cu-catalyzed *O*-arylation and Pd-catalyzed *C*-arylation (Scheme 34). Treatment of 2-iodobenzoic acid (**147**) with isocyanide **148** along with different aldehydes and amines resulted in the formation of Ugi adducts **149**, which underwent intramolecular O-cyclization in the presence of CuI (5 mol%) and thiophene-2-carboxylic acid (**150**) under heating conditions to give benzoxazole intermediates **151** in poor to quantitative yields. The resulting intermediates **151** were readily converted into products **152** via Pd-catalyzed C-arylation.

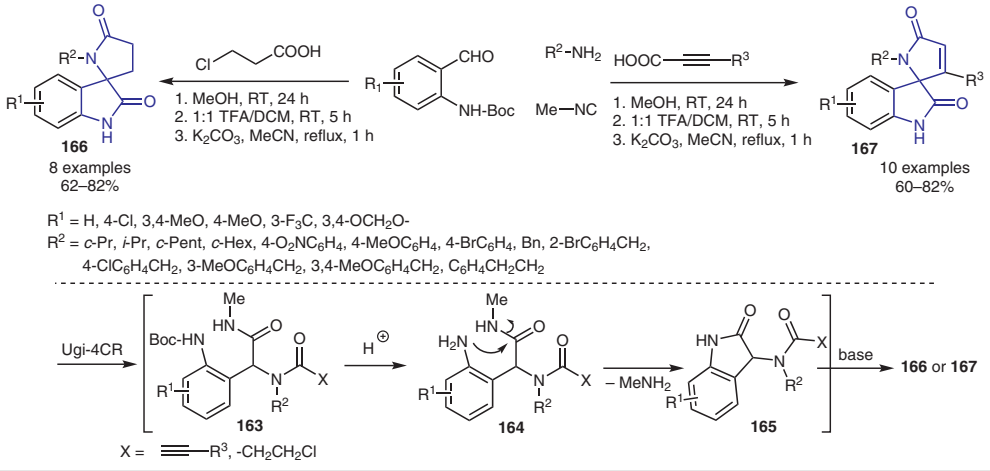


Scheme 35 DOS of polycyclic benzo-fused γ-lactams **161** and **162**

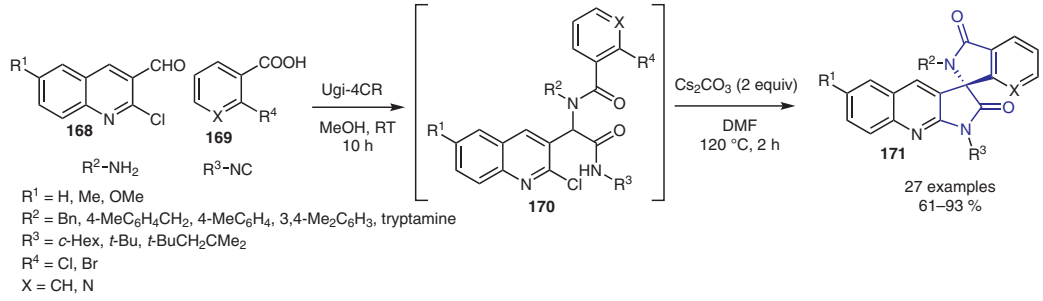
In 2015, a diversity-oriented synthesis (DOS) approach towards polycyclic benzo-fused γ-lactams **161** and **162** was carried out via palladium-catalyzed C–C bond formation as the key step (Scheme 35).[77] Initially benzoyloxyacetaldehyde **153**, 2-iodobenzoic acid **154**, and isocyanides were reacted with allyl/homoallyl amines **155** or benzylamine/heteroaromatic methenamines **158** via a Ugi-4CR. This was followed by base-mediated elimination of the benzoate group to give dehydroalanine adducts **156** and **159**. The adduct **156** underwent a Pd-catalyzed double 5-*exo*-*trig*/Heck cascade cyclization when the amine input was allylamine or a 5-*exo*-*trig*/6-*exo*-*trig* Heck reaction in the case of a homoallyl amine to give tricyclic benzo-fused γ-lactams **162**. With benzylamines, 5-*exo*/C–H insertion took place to afford the tetracyclic benzo-fused γ-lactams **161**. The reaction might follow a conventional intramolecular Heck reaction pathway. Initially, oxidative addition occurs followed by intramolecular alkene insertion to generate Pd complexes **157** and **160**. Next, complex **157** undergoes a second intramolecular alkene insertion and β-hydride elimination to afford the final cyclized product **162**. On the other hand, complex **160** undergoes C–H oxidative insertion to give product **161**.

2.3.3 Spiro-γ-Lactams

In 2018, Andreana and Maddirala[78] developed an efficient DOS of spirocyclic γ-lactams **166** and α,β-unsaturated γ-lactam oxindoles **167** in good to excellent yields via a one-pot, three-step post-Ugi domino transformation/cyclization strategy (Scheme 36). This three-step sequential strategy started with an Ugi-4CR followed by an acid-promoted intramolecular transamidation and finally a base-



Scheme 36 DOS of spirocyclic γ-lactam **166** and α,β-unsaturated γ-lactam oxindoles **167**



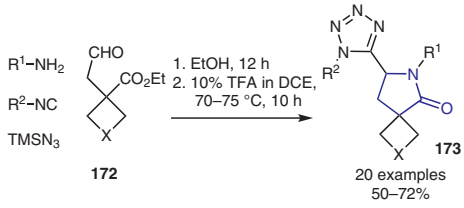
Scheme 37 Synthesis of functionalized spirocyclic γ-lactam scaffolds **171**

mediated cyclization to give spirocyclic γ-lactams **166** and α,β-unsaturated γ-lactam oxindoles **167**. The acid-mediated Boc deprotection of Ugi intermediate **163** resulted in the generation of aniline intermediate **164**, which subsequently cyclized through an intramolecular transamidation process to yield compound **165** and methylamine as a byproduct. Next, compound **165** underwent a K_2CO_3-mediated intramolecular cyclization via an S_N2 process to afford target compounds **166** when the acid component was 1-chloropropionic acid and compounds **167**, via 5-*endo*-*dig* cyclization, when propiolic acid was used.

In 2015, the group of Ghandi published an efficient one-pot strategy for the synthesis of functionalized spirocyclic γ-lactam scaffolds **171** via an Ugi-4CR followed by two consecutive post-condensation intramolecular C–C and N–C cyclizations, respectively (Scheme 37).[79] The developed strategy utilizes electron-deficient substituted 2-chloroquinoline-3-carbaldehydes **168**, amines, 2-chloronicotinic acid or 2-bromobenzoic acid **169** and isocyanides to generate in situ an Ugi product **170** containing four reactive sites. Further, adduct **170** undergoes two bis-annulation post-Ugi processes in the presence of the base Cs_2CO_3 (2 equiv) to give the final spirocyclic γ-lactams **171** in excellent yields. The structures of the synthesized products were confirmed by single-crystal X-ray-diffraction analysis.

Stolyarenko and co-workers[80] reported the synthesis of 1,5-disubstituted-tetrazole-linked spirocyclic γ-lactams **173** via a one-pot, two-step Ugi–azide MCR process (Scheme 38). The authors effectively utilized bifunctional γ-oxo ester reagents **172** with several amines, isocyanides and $TMSN_3$ to obtain the Ugi adducts, which were further reacted under acidic conditions to give the final products **173** in moderate to good yields (50–72%). The products **173** were characterized by X-ray analysis.

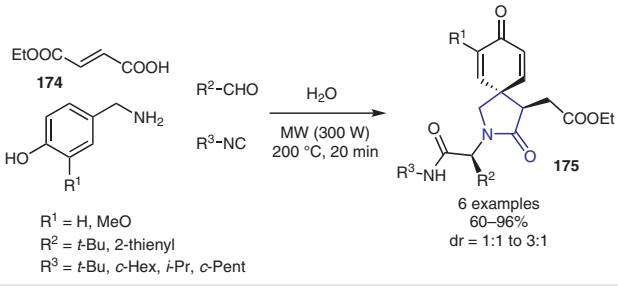
Andreana and Santra reported the synthesis of spirocyclic γ-lactam cyclohexadienones **175** via an Ugi-4CR followed by a 5-*exo*-*trig* Michael cyclization using water as the solvent under microwave irradiation (300 W) at 200 °C (Scheme 39).[25] It is important to note that the highly complex spirocyclic γ-lactam products **175** were synthesized in excellent yields by using bifunctional carboxylic acid **174** as



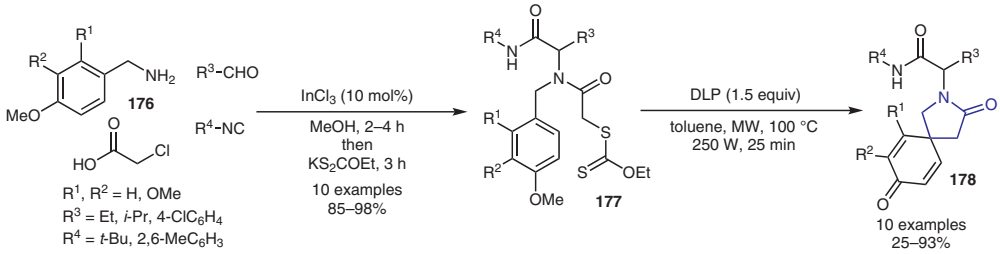
Scheme 38 Synthesis of 1,5-disubstituted-tetrazole-linked spirocyclic γ-lactams **173**

the substrate without using any additive. Also, it was noted that transition state stabilization by H_2O, the sterics of the carboxylic acid substrate, and the presence of an electron-donating group on the amine influenced the formation of spirocyclic-γ lactam scaffolds **175** with the help of MW heating.

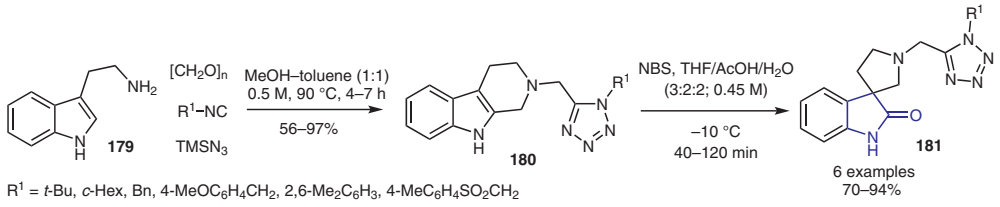
Another outstanding example of the synthesis of spirocyclic γ-lactam cyclohexadienones **178** was described by Gámez-Montaño and colleagues[81] via a two-step Ugi-4CR followed by microwave-assisted radical cyclization (Scheme 40). Reaction of benzylamine **176**, an aldehyde, chloroacetic acid, and an isocyanide followed by addition of the potassium salt of xanthic acid (KS_2COEt) resulted in the generation of Ugi xanthate adduct **177**. Next, microwave-assisted radi-



Scheme 39 Synthesis of spirocyclic γ-lactam cyclohexadienones **175**



Scheme 40 Synthesis of spirocyclic γ-lactam cyclohexadienones **178**

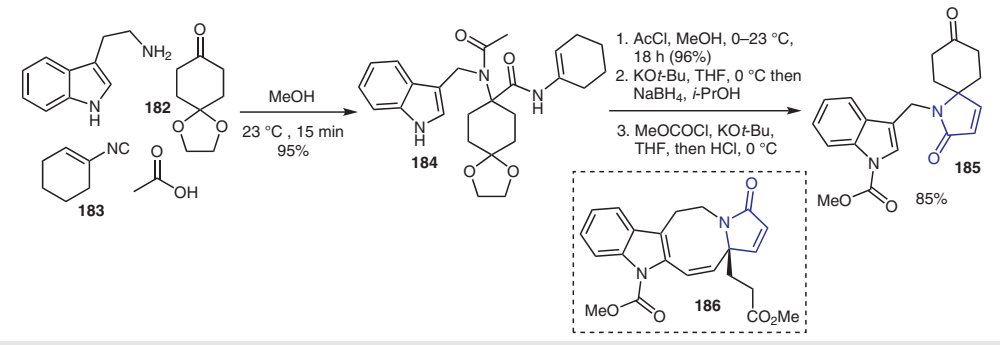


Scheme 41 A two-step synthesis of 1,5-disubstituted-linked spirocyclic γ-lactams **181**

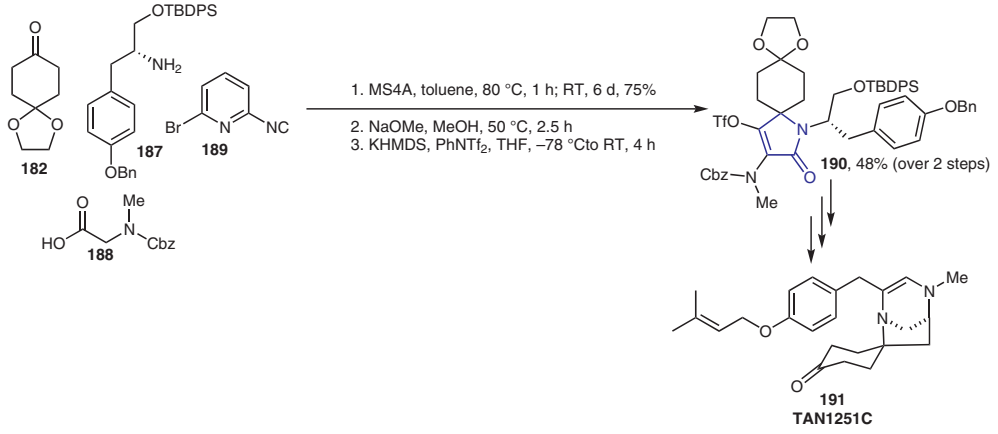
cal spirocyclization was performed to yield spirocyclic γ-lactam **178** in the presence of DLP as a radical initiator at 100 °C. It was noted that, inseparable diastereomeric mixtures (1:1 to 7:3) were obtained for the products where $R^1 \neq R^2$.

Later, in 2017, the same research group[82] synthesized 1,5-disubstituted linked spirocyclic γ-lactam oxindoles **181** via two experimental steps: (a) a one-pot Ugi–azide/Pictet–Spengler process coupled with (b) a one-pot oxidative spiro-rearrangement (Scheme 41). Initially, different isocyanides were reacted with tryptamine (**179**), formaldehyde, and $TMSN_3$ under heating conditions to afford bis- heterocyclic Ugi products **180**, which were further subjected to oxidative spiro-rearrangement in the presence of NBS under acidic conditions to give the spirocyclic-γ-lactam oxindoles **181**. It was noted that except for the benzyl isocyanide analogue, all the other products were formed in excellent yields. Cleavage of the benzylic group under oxidative conditions led to a lower yield of the benzyl isocyanide analogue (70%).

Due to their versatility and flexibility, MCRs are important in numerous areas of chemistry including the total synthesis of natural products.[83] An efficient example of the synthesis of the natural product **186** containing an α,β-unsaturated γ-lactam core by the effective use of a convertible isocyanide-based Ugi reaction as the key step was disclosed by Sarpong and co-workers in 2012.[84] Convertible isocyanides are a class of isocyanides that can be transformed into various functionalities once the condensation product has been formed.[85] As a result, the use of convertible isocyanides in natural product synthesis has increased. Sarpong reported the synthesis of fused polycyclic α,β-unsaturated γ-lactam **186**, a base core found in the *Kopsia* alkaloids lapidilectine B, grandilodine C, and tenuisine A, from spirocyclic α,β-unsaturated γ-lactam intermediate **185**, itself obtained via an Ugi-4CR (Scheme 42). The Ugi-4CR between tryptamine (**179**), cyclohexanone **182**, convertible isocyanide **183**, and acetic acid in MeOH resulted in the formation of Ugi adduct **184** in 95% yield. Subsequent esterification,



Scheme 42 Synthesis of spirocyclic α,β-unsaturated γ-lactam intermediate **185**



Scheme 43 Synthesis of spirocyclic α,β-unsaturated γ-lactam triflate **190**

Dieckmann condensation, $NaBH_4$ reduction and intramolecular elimination afforded key intermediate **185** in an overall yield of 85%.

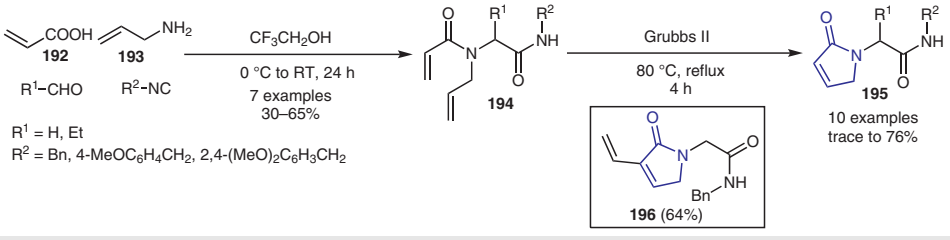
Another elegant example of the efficient use of a convertible isocyanide-based Ugi reaction in the synthesis of the natural product TAN1251C (**191**) was published by Kan and co-workers (Scheme 43).[86] Initially, an Ugi-4CR between cyclohexanone **182**, amine **187**, N-protected amino acid **188** and 2-bromo-6-pyridine isocyanide (**189**) resulted in the formation of the corresponding Ugi adduct in 75% yield, which upon sodium methoxide mediated Dieckmann condensation at 50 °C followed by addition of triflic imidate in the presence of excess KHMDS afforded key spirocyclic α,β-unsaturated γ-lactam triflate intermediate **190** in 48% overall yield. Next, key intermediate **190** was readily converted into the desired natural product TAN1251C (**191**) after performing several multistep reactions.

2.3.4 α,β-Unsaturated γ-Lactams

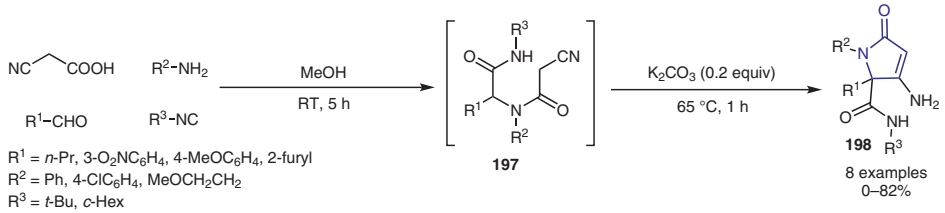
The combination of an Ugi-4CR and ring-closing metathesis was described by Keum and colleagues (Scheme 44).[87] Here, adducts **194** were formed in good yields after Ugi-4CRs between acrylic acid (**192**), allylamine (**193**), aldehydes, and isocyanides at 0 °C to room temperature. Subsequently, ruthenium-catalyzed ring-closing olefin metathesis resulted in the formation of α,β-unsaturated γ-lactams **195**. Optimization studies revealed that 5 mol% of the Grubbs catalyst in either toluene or benzene was sufficient for the metathesis reaction to give the expected cyclized products **195**. When propargylamine was used, vinyl-substituted γ-lactam **196** was obtained in 64% yield via a two-step Ugi-4CR/enyne metathesis reaction.

A small series of α,β-unsaturated γ-lactams **198** was synthesized by the group of El Kaïm[88] via an Ugi-4CR followed by base-mediated intramolecular cyclization in a one-pot manner (Scheme 45). The formation of the product was highly dependent on the acidity of the peptidyl tertiary proton of the Ugi intermediate **197**. Substituted aromatic or heteroaromatic aldehydes offered sufficiently acidic peptidyl protons and hence were well tolerated in the reaction, in contrast to butyraldehyde which failed to give the cyclized product even after prolonged heating.

In 2014, Van der Eycken and co-workers[89] disclosed the synthesis of α,β-unsaturated γ-lactams **201** via a one-pot Ugi-4CR followed by 5-*endo*-*dig* carbocyclization and retro-Claisen fragmentation at 80 °C (Scheme 46). The authors used 3-substituted propiolic acids and phenyl glyoxals along with different amines and isocyanides to give Ugi adducts **199**. Further, the intermediates **199** spontaneously underwent a 5-*endo*-*dig* carbocyclization to afford γ-lactams **200**, which were subsequently converted into the final

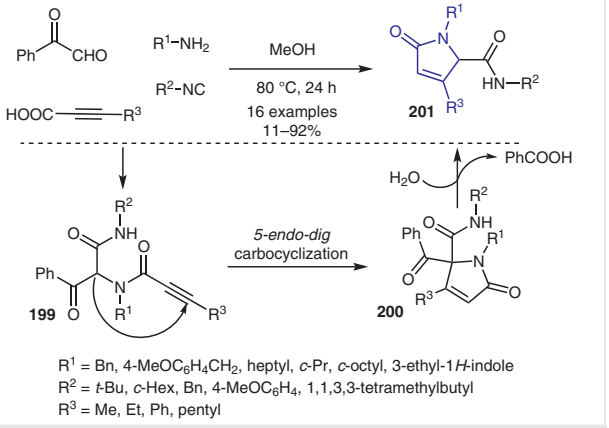


Scheme 44 Synthesis of α,β-unsaturated γ-lactams **195**



Scheme 45 Synthesis of α,β-unsaturated γ-lactams **198**

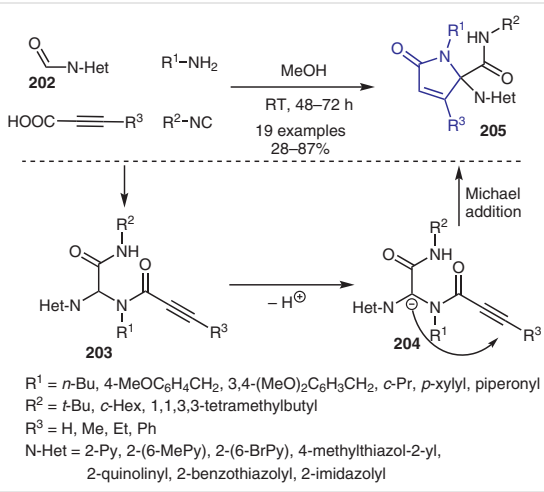
α,β-unsaturated γ-lactams **201** via retro-Claisen fragmentation through cleavage of the benzoyl moiety. The presence of an additional electron-withdrawing (carbonyl) group next to the enolizable tertiary carbon and the Michael acceptor nature of a triple bond conjugated with an amide triggered the 5-*endo*-*dig* carbocyclization to give intermediate **200**. The authors demonstrated the importance of the electron-withdrawing carbonyl group by replacing the phenyl glyoxal with paraformaldehyde, the reaction of which gave only the acyclic Ugi adduct without the formation of the desired cyclized final product.



Scheme 46 Synthesis of α,β-unsaturated γ-lactams **201** via a one-pot Ugi-4CR/5-*endo*-*dig* carbocyclization/retro-Claisen fragmentation strategy

Later, in 2016, the same research group demonstrated the synthesis of highly substituted α,β-unsaturated γ-lactams **205** via a domino Ugi-4CR/Michael process starting from nitrogen-containing heterocyclic aldehydes **202**, amines, 2-alkynoic acids and isocyanides (Scheme 47).[90] Initially the Ugi adduct **203** formed with the nitrogen heterocycle acting as a base to generate carbanion **204**. This intermediate then underwent a Michael addition to afford the final product **205**. A lower yield (32%) was observed with 6-bromopicolinaldehyde, even after heating at 50 °C. The authors used this protocol to synthesize a variety of substituted α,β-unsaturated γ-lactams in a one-pot manner.

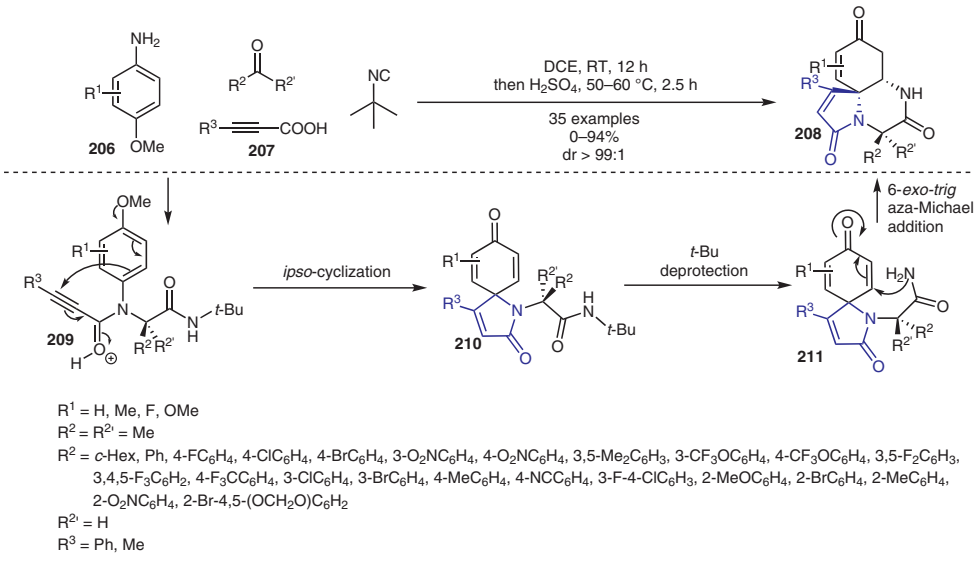
In 2016, Srivastava and co-workers[91] prepared a series of alkaloid-like tricyclic α,β-unsaturated γ-lactams **208** via a one-pot Ugi-4CR, acid-mediated *ipso*-cyclization and an



Scheme 47 Synthesis of highly substituted α,β-unsaturated γ-lactams **205**

aza-Michael addition (Scheme 48). The authors utilized a variety of substituted 4-methoxyanilines **206** as amine substrates, aldehydes or ketones, propiolic acids **207** and *tert*-butyl isocyanide to afford Ugi-adducts **209**. These adducts underwent acid-catalyzed intramolecular *ipso*-cyclization in a 5-*endo*-*dig* manner to generate spirocyclic α,β-unsaturated γ-lactam intermediates **210**. Cleavage of the *tert*-butyl group with excess H_2SO_4 then afforded acetamides **211** that yielded the tricyclic α,β-unsaturated γ-lactam products **208** via an intramolecular aza-Michael addition proceeding through a 6-*exo*-*trig* route. It was noted that when cyclohexyl isocyanide was used, only spirocyclic intermediate **210** was isolated from the respective Ugi adduct after sulfuric acid treatment. Thus, the presence of a *tert*-butyl group was crucial, which after cleavage triggered the aza-Michael addition to give the final products.

In 2016, Van der Eycken and co-workers[92] developed an efficient two-step diversity-oriented synthetic strategy for the synthesis of fused tris-heterocyclic α,β-unsaturated γ-lactams **216** via a domino Ugi-4CR followed by a Michael addition reaction (Scheme 49). The disclosed methodology utilizes imidazole-2-carbaldehyde (**212**), propargyl amines **213**, 2-alkynoic acids **214**, and isocyanides to afford imidazo-linked α,β-unsaturated γ-lactams **215** through an Ugi-4CR/Michael addition in one-pot. Further, the $AgSbF_6$ (5



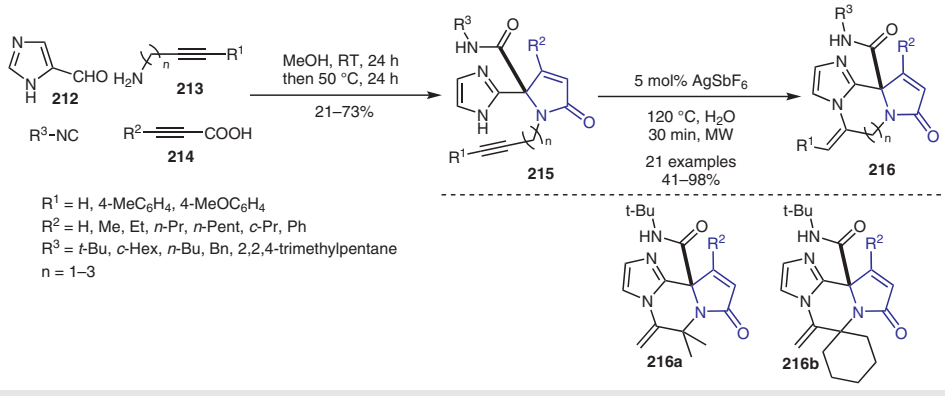
Scheme 48 Synthesis of alkaloid-like tricyclic α,β-unsaturated γ-lactams **208**

mol%) catalyzed intramolecular heteroannulation of intermediate **215** under aqueous conditions led to the synthesis of final products **216** in moderate to excellent yields. The authors offered 21 examples of this methodology, including the preparation of compounds **216a** and **216b** in which dimethyl- and cyclohexyl-substituted propargylamines were used, respectively. Furthermore, it was also claimed that this methodology could be performed in a one-pot, three-step fashion to furnish the final product **216** in an overall yield of 26%.

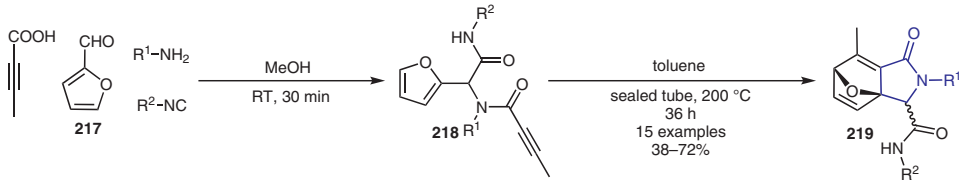
2.3.5 Fused-Polycyclic γ-Lactams

McCluskey and co-workers[93] reported the Ugi-4CR between an alkenoic acid, 2-furaldehyde (**217**), isocyanides, and amines in MeOH to afford acetylenic furan intermediates **218**, which upon heating at 200 °C in a sealed tube underwent an intramolecular Diels–Alder reaction to give fused tricyclic γ-lactams **219** in moderate to good yields (Scheme 50). It was noted that lower yields were obtained when *N*,*N*-dimethylaminopropylamine was used due to proton scavenging of the acid by a tertiary amine group. In this case, the addition of 2 equivalents of the alkenoic acid resulted in formation of the final tricyclic product **219** in 72% yield. A disadvantage of this protocol was the requirement of an extremely high temperature (200 °C) for a longer time period (36 h).

Santra and Andreana[94] reported the synthesis of natural-product-like fused polycyclic bis-lactams **222** by using an Ugi-4CR/Michael/aza-Michael cascade reaction in a one-pot manner (Scheme 51). It was noted that the bulky nature of the R^1 substituent on the carboxylic acid **221** and R^3 on the isocyanide substrate played an important role in the formation of products **222**, **223**, and **224**. A less bulky group (NHMe) at R^1 led to the synthesis of fused tricyclic γ-lactam **223** through a 6-*exo*-*trig* aza-Michael route. However, the

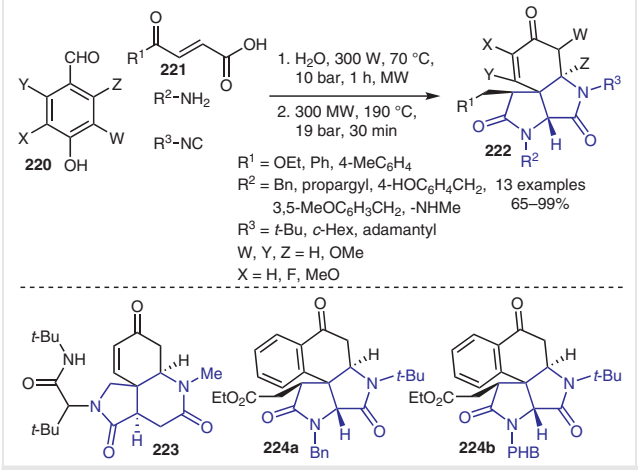


Scheme 49 Synthesis of fused tris-heterocyclic α,β-unsaturated γ-lactams **216**



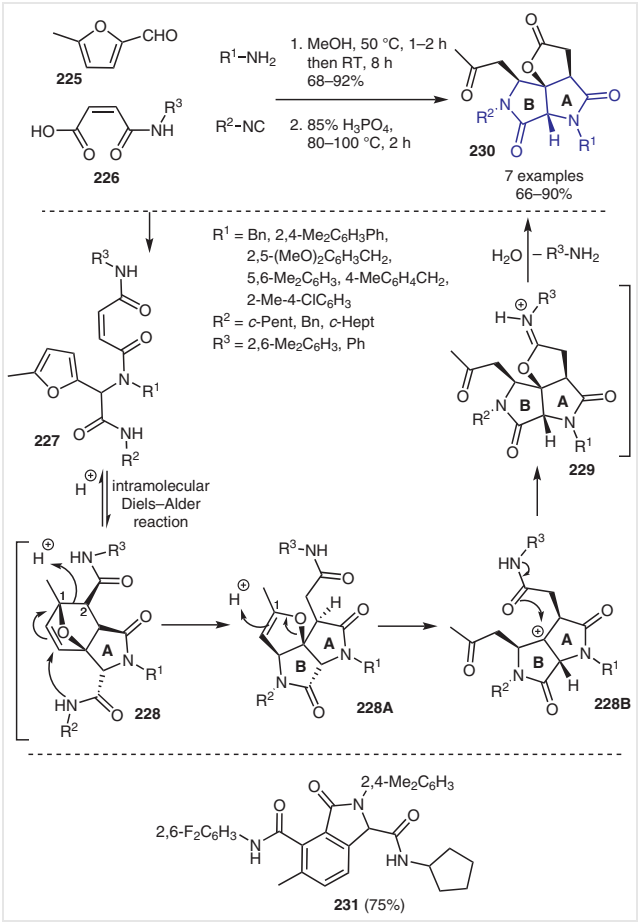
Scheme 50 Synthesis of fused tricyclic γ-lactams **219**

presence of bulky R^3 substituents led to a 5-*exo-trig* aza-Michael path being followed as a result of the proximity effect instead of a 6-*exo-trig* aza-Michael addition, thus ultimately giving rise to fused tricyclic bis-γ-lactam **222** and fused tetracyclic bis-γ-lactam **224** products.



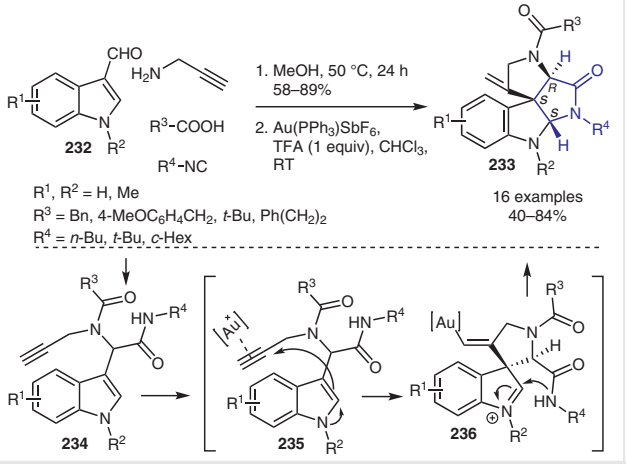
Scheme 51 Synthesis of natural-product-like fused polycyclic bis-lactams **222**

In 2006, Ivachtchenko and co-workers[95] demonstrated the synthesis of diastereomerically pure natural-product-like fused tricyclic bis-γ-lactams **230** via an Ugi-4CR/intramolecular Diels–Alder (IMDA) sequence followed by an unexpected acid-mediated rearrangement (Scheme 52). Initially, 5-methylfuran-2-carbaldehyde (**225**), maleic acid monoamides **226**, amines, and isocyanides were reacted together under heating to give bicyclic bridged adduct **228** fused with a newly formed γ-lactam ring (**A**) from Ugi intermediate **227** via a one-step Ugi-4CR/IMDA sequence. The acid-mediated rearrangement mechanism proposed by the authors began with heterolytic cleavage of the C1–C2 bond in the intermediate **228** assisted by the secondary amide side chain, leading to the generation of transient intermediate **228A** with another γ-lactam ring (**B**) and a hydrolytically prone cyclic enol ether moiety. Subsequent acid-promoted opening of the cyclic enol ether of **228A** led to the generation of carbocation **228B**, which was followed by carbocation trapping by the amide carbonyl side chain and hydrolysis resulting in the formation of tricyclic fused bis-γ-lactam product **230** with loss of the R^3-NH_2 group (Scheme 52). It was also claimed that treatment of the Ugi-4CR/IMDA product **228** with a catalytic amount of the Lewis acid $BF_3{\cdot}Et_2O$ in a *nonpolar medium* resulted in the formation of fused-benzo-γ-lactam **231** in 75% yield via aromatization and with no rearrangement product being detected.



Scheme 52 Synthesis of natural-product-like fused tricyclic bis-γ-lactams **230**

Van der Eycken and co-workers[96] reported the synthesis of fused tetracyclic γ-lactams **233** via an Ugi-4CR followed by a gold-catalyzed cyclization in a two-step process (Scheme 53). First, they reacted 3-formylindoles **232** and propargylamine with a variety of carboxylic acids and isocyanides to give Ugi products **234** in moderate to excellent yields (58–89%). Adducts **234** were then subjected to an $Au(PPh_3)SbF_6$ (5 mol%) catalyzed domino cyclization to furnish the products **233** in moderate to excellent yields. The Au-catalyzed cyclization mechanism proposed by the authors began with intramolecular frontal *exo-dig* attack of the indole core on the terminal alkyne (intermediate **235**), which was activated by cationic Au-coordination. This was followed by amidic NH trapping of the iminium ion (intermediate **236**) and protodeauration resulted in the formation of product **233** with *S* stereochemistry at two of the newly formed stereocenters.

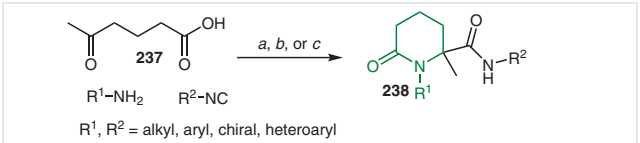


Scheme 53 Synthesis of fused tetracyclic γ-lactams **233** via an Ugi-4CR/gold-catalyzed cyclization

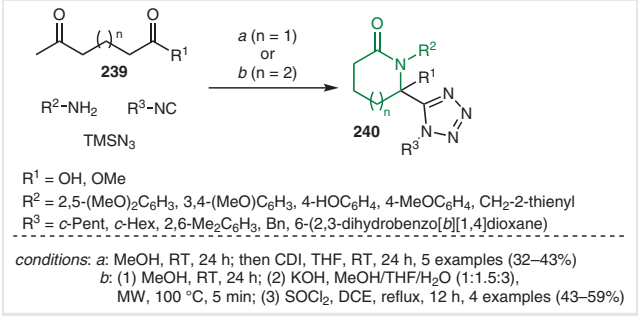
2.4 δ-Lactams

In 2010, Deprez and co-workers[50] reported the synthesis of δ-lactams **238** by using bifunctional 5-ketohexanoic acid (**237**), amines, and isocyanides via an Ugi-3CR under solvent-free microwave heating conditions at 100 °C (Scheme 54). It was noted that this methodology gave higher yields of δ-lactams in shorter reaction times compared to the previously published lengthy conventional methods,[48,51] where the key Mumm rearrangement step occurs via a less favorable seven-membered cyclic transition state, thus resulting in lower yields.

In 2012, Hulme and co-workers[97] synthesized two series of 1,5-disubstituted tetrazole-linked δ- and ε-lactams **240** via a one-pot Ugi–azide reaction followed by intramolecular amide formation (Scheme 55). For the synthesis of δ-lactams, 5-oxohexanoic acid **239** (R^1 = OH, n = 1) was reacted with amines, isocyanides, and $TMSN_3$ in MeOH at room temperature. A subsequent 1,1′-carbonyldiimidazole (CDI) mediated intramolecular amidation in THF then gave the δ-lactam products in moderate yields (conditions a). On the other hand, ε-lactams were obtained by reacting methyl 6-oxoheptanoate **239** (R^1 = OMe, n = 2), amines, isocyanides, and $TMSN_3$ under conventional Ugi–azide reaction conditions to give the expected Ugi adducts, which upon base-mediated hydrolysis followed by $SOCl_2$ activation were readily converted into seven-membered cyclic ε-lactams after 12 hours at reflux (conditions b).

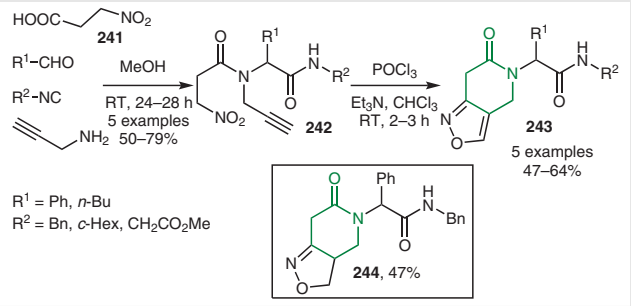


Scheme 54 Synthesis of δ-lactams **238**



Scheme 55 Synthesis of 1,5-disubstituted tetrazole-linked δ- and ε-lactams **240**

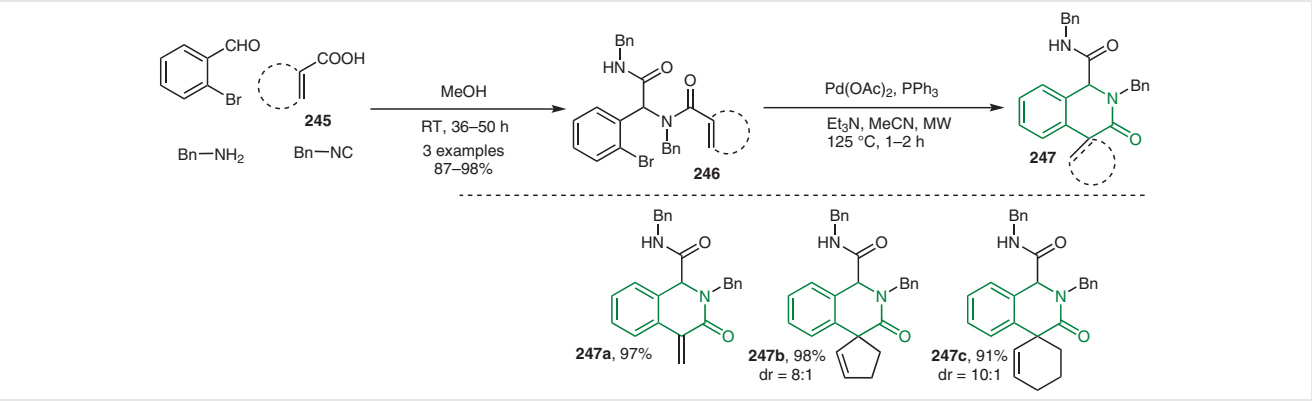
In 2004, Akritopoulou-Zanze and co-workers[98] synthesized isoxazole-fused δ-lactams **243** in good yields via a two-step Ugi-4CR/intramolecular nitrile oxide cycloaddition reaction (Scheme 56). First, the Ugi adducts **242** were synthesized by reacting nitro-substituted carboxylic acid **241**, propargylamine, aldehydes, and isocyanides in methanol, which upon treatment with $POCl_3$ in the presence of Et_3N afforded products **243** via an intramolecular [3+2] nitrile oxide cycloaddition. When allylamine was used instead of propargylamine under similar reaction conditions, isoxazoline-fused δ-lactam **244** was obtained in 47% yield. It was reported that the use of excess $POCl_3$ and Et_3N resulted in the decomposition of the product, thus giving lower yields.



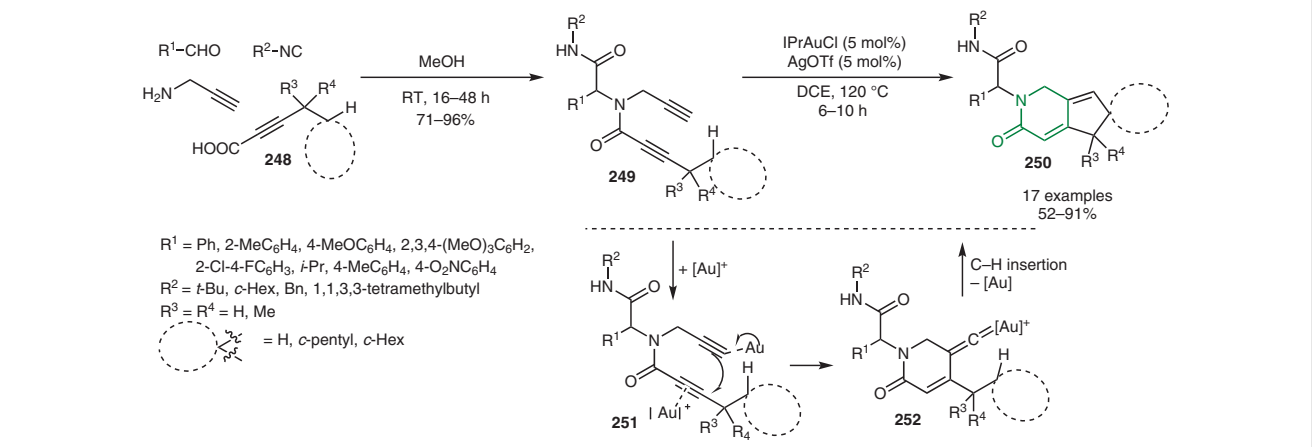
Scheme 56 Synthesis of isoxazole-fused δ-lactams **243**

Gracias and co-workers[99] have synthesized benzo-fused δ-lactams **247** in quantitative yields via an Ugi-4CR followed by a microwave-assisted intramolecular Heck reaction (Scheme 57). This two-step sequential protocol started with the reaction between 2-bromobenzaldehyde, cyclic or acyclic α,β-unsaturated carboxylic acids **245**, benzylamine and benzyl isocyanide to give Ugi adducts **246** in excellent yields. Next, adducts **246** underwent a Pd-catalyzed intramolecular Heck cyclization under microwave heating at 125 °C to generate the cyclized products **247** in excellent yields (91–97%). The use of cyclic α,β-unsaturated carboxylic acids led to the formation of spirocyclic benzo-fused δ-lactams **247b** and **247c** with excellent stereoselectivities. It was noted that the reaction times for the Heck cyclization were greatly reduced and increased yields of the cyclized products were obtained under microwave heating conditions.

In 2013, Van der Eycken and co-workers[100] reported an efficient synthesis of spirocyclopenta-fused and cyclopenta-fused δ-lactams **250** via a two-step Ugi-4CR followed by gold-catalyzed regioselective tandem cyclization through Csp^3–H functionalization (Scheme 58). A multicomponent reaction between propargylamine, alkynoic acid **248**, aldehydes, and isocyanides gave Ugi adducts **249** in excellent yields. Adducts **249** were then subjected to an intramolecular gold-catalyzed tandem cyclization under heating conditions to afford the cyclized products **250** in 52–91% yields. A plausible reaction mechanism was proposed in which the first step is the formation of a gold acetylide π-activated butynamide intermediate **251**. Subsequent catalytic transfer followed by a 6-*endo*-*dig* cyclization leads to the gold vi-



Scheme 57 Synthesis of benzo-fused δ-lactams **247**

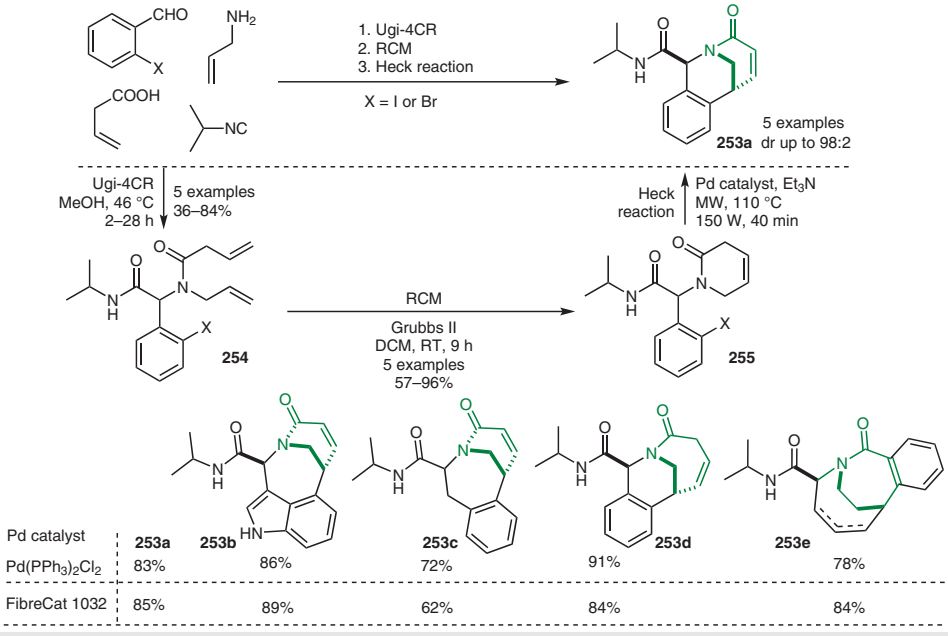


Scheme 58 Synthesis of spirocyclopenta-fused and cyclopenta-fused δ-lactams **250**

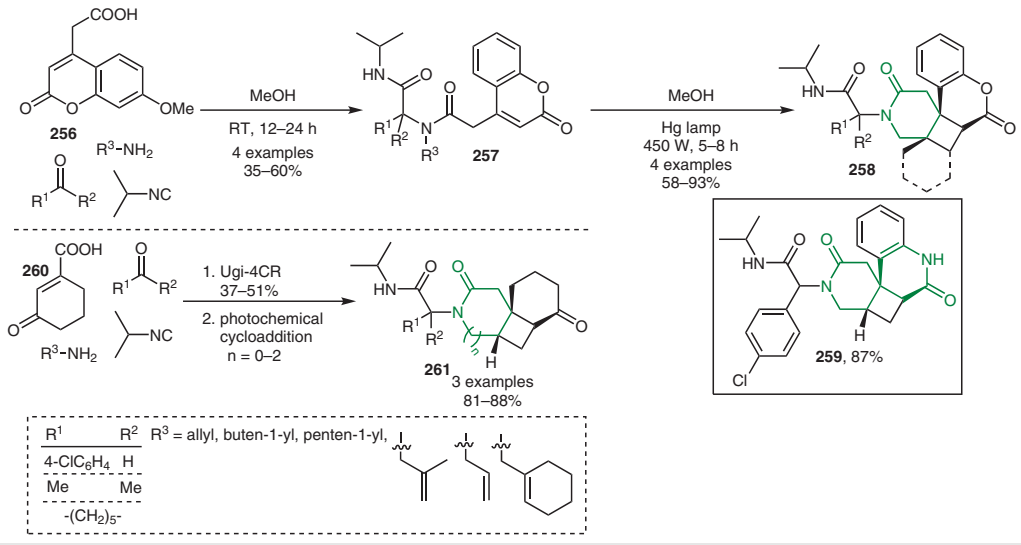
nylidene intermediate **252**. Next, this highly reactive species may undergo C–H insertion and protodeauration to give the final product **250**.

In 2007, Judd and co-workers[101] synthesized a small library of bridged bicyclic six- and seven-membered lactams **253**, with high (up to 98:2) diastereoselectivity, via a three-step Ugi-4CR/ring-closing metathesis/Heck reaction strategy (Scheme 59). Initially, the four-component Ugi reaction between different aldehydes, an amine, a carboxylic acid, and isopropyl isocyanide was carried out to give diene Ugi adducts **254** in moderate to excellent yields, which underwent ring-closing metathesis in the presence of the Grubbs second-generation catalyst to give unsaturated δ-lactams **255** in excellent yields. Subsequent intramolecular Heck reaction of **255** using two different Pd catalysts [$Pd(PPh_3)_2Cl_2$ or FibreCat 1032] resulted in the formation of complex bridged bicyclic δ-lactams **253a–c** and ε-lactams **253d**,**e**. It was noted that the Heck reaction was well tolerated and equally efficient in the presence of both catalysts.

Akritopoulou-Zanze's group[102] reported the synthesis of polycyclic fused δ-lactams **258** via a two-step Ugi-4CR of chromenone acetic acid **256**, aldehydes or ketones, amines,



Scheme 59 Synthesis of bridged bicyclic δ-lactams and ε-lactams **253**



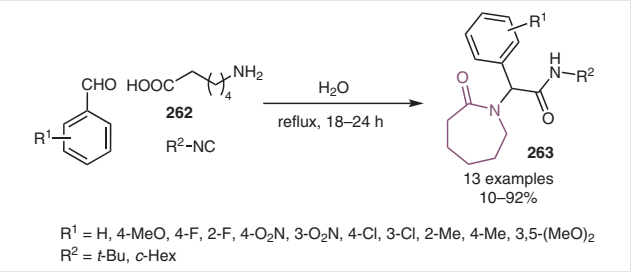
Scheme 60 Synthesis of polycyclic fused δ-lactams **258**, **259** and **261**

and isopropyl isocyanide to initially give Ugi adducts **257**. This was followed by a [2+2] enone–alkene photochemical cycloaddition in MeOH using a 450 W mercury lamp (Scheme 60). Using dihydroquinoline acetic acid instead of acid **256**, the authors were able to easily prepare polycyclic fused bis-δ-lactam **259** in 87% yield. Switching the acid source **256** to oxo-cyclohexene acid **260** and the substituted allylamine to long-chain amines resulted in the formation of tricyclic fused γ-, δ- and ε-lactams **261** in excellent yields.

2.5 ε-Lactams

Foroumadi and colleagues[103] reported the synthesis of ε-lactams **263** by employing 6-aminohexanoic acid (**262**), aldehydes, and isocyanides in Ugi-3CRs in water under reflux conditions for 18–24 hours (Scheme 61). It was noted that no product formation was observed when the reactions were performed at ambient temperature. *ortho*-Methyl-substituted benzaldehyde gave the lowest yield (10%), suggesting that steric effects play an important role in the reaction. The mild and green reaction conditions are advantages of this methodology.

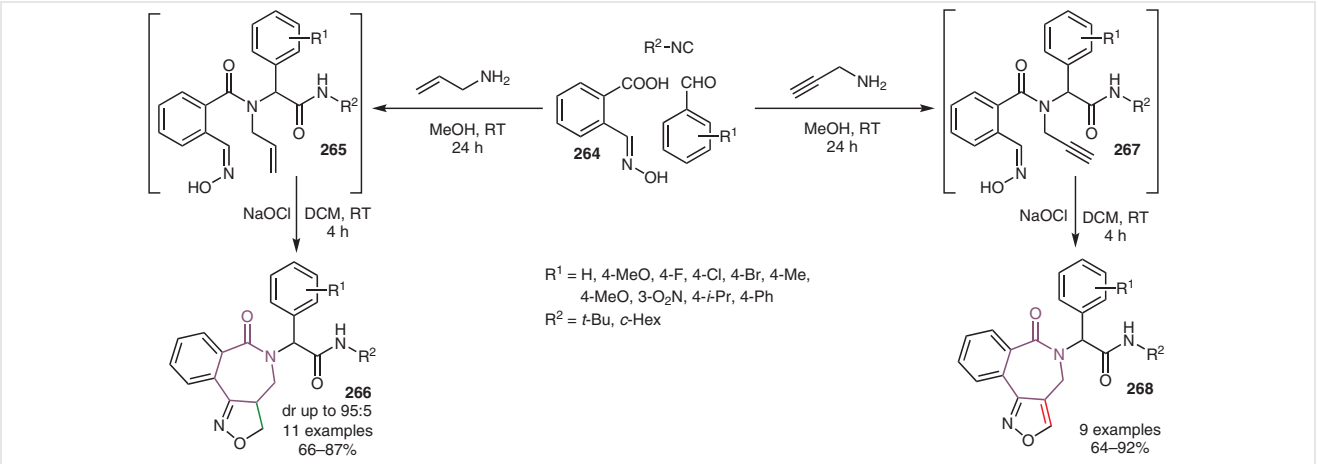
In 2017, Balalaie and co-workers[104] reported the diversity-oriented synthesis of isoxazolino- and isoxazolo-fused ε-lactams **266** and **268** via a one-pot Ugi-4CR followed by an intramolecular 1,3-dipolar cycloaddition (Scheme 62). It was demonstrated that the four-component reaction between functionalized acid **264**, an aldehyde, an isocyanide, and either allylamine or propargylamine in MeOH at ambient temperature gave the Ugi adducts **265** or **267**, respectively. Subsequently, intramolecular 1,3-dipolar cycloaddition resulted in the formation of ε-lactams **266** and **268** in good to excellent yields. It was noted that all the synthesized ε-lactams were obtained with high diastereoselective ratios.



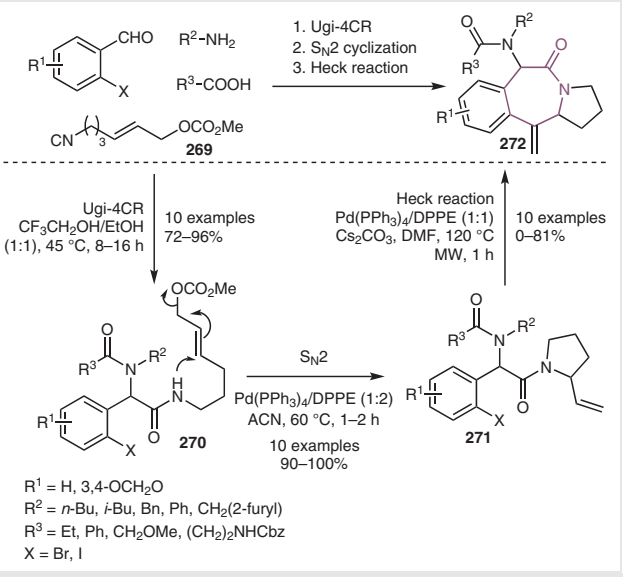
Scheme 61 Synthesis of ε-lactams **263**

Riva and co-workers[105] have reported the synthesis of fused polycyclic natural-product-like molecules **272** containing a 7-membered lactam core via an Ugi-4CR/S_N2 cyclization/Heck reaction methodology (Scheme 63). The Ugi adducts **270** were prepared in excellent yields (72–96%) by reacting aldehydes, polyfunctionalized isocyanide **269**, amines, and acids in a mixture of trifluoroethanol–ethanol (1:1) . Next, the adducts **270** were readily converted into compounds **271** in quantitative yields via intramolecular S_N2 carbocyclization using a $Pd(PPh_3)_4$–DPPE catalytic system. Subsequently, a microwave-assisted Pd-catalyzed intramolecular Heck reaction afforded the fused polycyclic lactams **272** in poor to excellent yields (0–81%). It was noted that the nature of the halogen atom on the aldehyde influenced the Heck cyclization. When iodo derivatives were used, the cyclization was cleaner and high yielding compared to the bromo derivatives. Also, it was reported that a one-pot S_N2/Heck cyclization sequence gave comparable yields of lactams **272** (from Ugi adducts **270**) to those obtained via the two-step method.

In 2013, Gámez-Montaño and co-workers[106] reported the synthesis of 1,5-disubstituted-tetrazole-linked polycyclic ε-lactams **274** in moderate to excellent yields via a two-step Ugi-4CR/N-acylation/S_N2 strategy, followed by an intramolecular radical cyclization (Scheme 64). Initially, an Ugi-4CR between tryptamine (**179**), aldehydes, isocyanides, and $TMSN_3$ was followed by the addition of KSC(S)OEt to



Scheme 62 Synthesis of isoxazolino- and isoxazolo-fused ε-lactams **266** and **268**



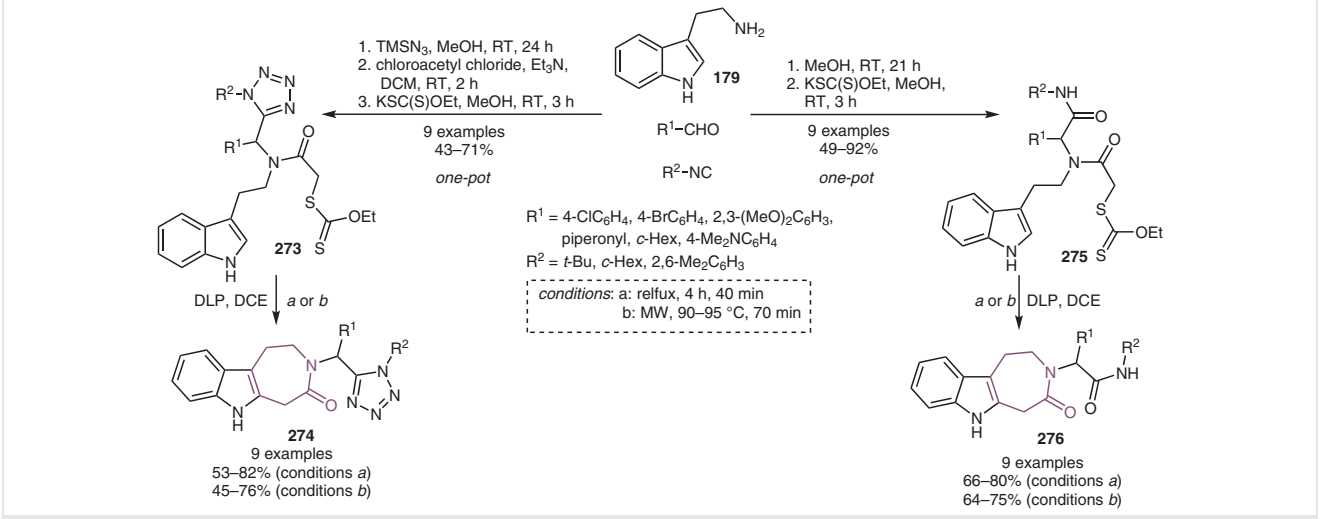
Scheme 63 Synthesis of fused polycyclic seven-membered lactams **272**

give Ugi xanthate adducts **273**, which on radical cyclization afforded ε-lactams **274**. All the reactions gave comparable yields of **274** when performed using two different conditions, i.e., conventional heating and microwave irradiation. It was proposed, based on docking studies, that these synthesized compounds could inhibit the 5-Ht_6 protein and thus might be useful in the discovery of anti-Alzheimer drugs. Later, in 2016, the same researchers[107] demonstrated the synthesis of amide-linked ε-lactams **276**, as bioisosteres of 1,5-disubstituted tetrazole lactams **274**, via Ugi-4CR/S_N2/radical cyclization under similar reaction conditions. The authors performed a comparative protein-binding affinity study between the two lactam series with the help of computational calculations, which suggested that lactams **276** showed a slight increased binding affinity towards the 5-Ht_6R protein compared to lactams **274**.

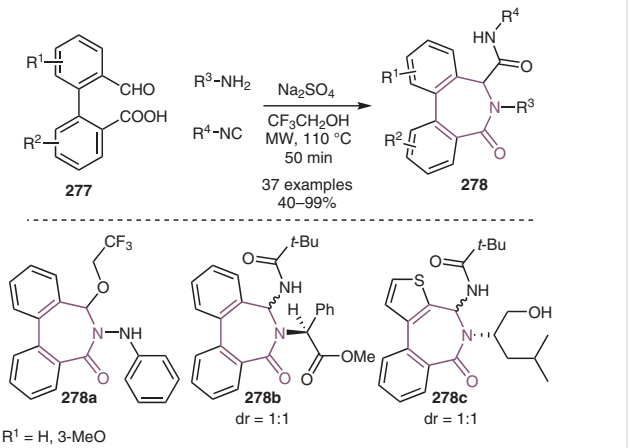
In 2011, Van der Eycken and co-workers[108] reported the diastereoselective synthesis of biaryl-fused ε-lactams **278** via an intramolecular four-centered Ugi-3CR by using bifunctional biaryls **277** (Scheme 65). A multicomponent reaction between 2′-formylbiphenyl-2-carboxylic acids **277**, amines and isocyanides in the presence of sodium sulfate in 2,2,2-trifluoroethanol at 110 °C under microwave irradiation afforded the ε-lactams **278** in moderate to quantitative yields (40–99%). The authors demonstrated 37 examples of this methodology including the synthesis of ε-lactam **278a** when phenylhydrazine was used as the amine input. Further, when the chiral amines (*S*)-(+)-2-phenylglycine methyl ester and L-leucinol were used, ε-lactams **278b** and **278c** were obtained in 64% and 40% yields, respectively, both with 1:1 diastereomeric ratios. All the synthesized compounds were screened against various DNA and RNA viruses, however, none of them were found to be active. Further, when the same series was tested for their antiproliferative activity, several promising compounds were found to be active against tumor cell lines in the lower micromolar range.

3 Conclusions

In conclusion, this review has summarized the advances made in the synthesis of lactams via isocyanide-based multicomponent reactions (IMCRs) in the last two decades. Huge progress has been accomplished in the synthesis of simple, highly substituted, unsaturated, polycyclic, fused and spiro lactams since the discovery of the β-lactam-containing antibiotic penicillin. However, there are several improvements that are still desired in this area. (1) The most useful reports on the synthesis of benzo-fused or polycyclic



Scheme 64 Synthesis of polycyclic ε-lactams **274** and **276**



R^1 = H, 3-MeO

R^2 = H, 6,7,8-$(MeO)_3$, 8-MeO

R^3 = *t*-Bu, *i*-Bu, *i*-Pr, 4-$MeOC_6H_4CH_2$, methyl-*c*-Pr, allyl, 3-$MeOC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, 2-$FC_6H_4CH_2$, 2,4,6-$Me_3C_6H_2CH_2$, 4-$HOC_6H_4CH_2CH_2$, 3,4-$(MeO)_2C_6H_4CH_2CH_2$, *n*-nonyl, *c*-Hex, *c*-Hept, 3,5-$Me_2C_6H_3CH_2$, 3-ethyl-1*H*-indolyl, propargyl, (*S*)-2-(4-methylpentan-1-ol), methyl (*S*)-2-(2-phenylacetate)

R^4 = *t*-Bu, *c*-Hex, 4-$MeOC_6H_4$, Bn, *n*-Pent, 4-$MeC_6H_4SO_2CH_2$, 9*H*-fluoren-9-yl, 2,3,3-trimethylbutane

Scheme 65 Synthesis of biaryl-fused ε-lactams **278** via an intramolecular Ugi-IMCR

lactams via C–N or C–H functionalization are largely dependent on expensive Pd or Au catalysts, hence, the development of new and inexpensive metal catalysts is required. (2) Despite α- and ε-lactam motifs being found in various bioactive molecules and natural products, there are only a few synthetic methods available via IMCRs. Thus, significant further developments towards their synthesis are required. (3) Most of the IMCR/post-transformation strategies often require high temperatures, long reaction times, and non-green conditions. Therefore, the development of mild, short, and eco-friendly reaction conditions is highly desirable. (4) IMCR or IMCR/post-transformation methodologies yielding asymmetric lactams are rare. Hence, the development of efficient asymmetric approaches towards chiral lactam analogues remains an important challenge.

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